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THREE CASES OF CONGENITAL CYANOSIS AFFECTING ALL CHILDREN IN A FAMILY AND A NEW METHOD OF DIAGNOSIS OF CONGENITAL HEART LESIONS*

JULIUS H. HESS, M.D., AND ROY G. PEARCE, M.D.
CHICAGO

These cases are presented primarily because of the rarity of the same anomaly affecting all children of a family.

The method by which we have arrived at an approximate diagnosis of the nature of the causative factor is presented as a preliminary report.

The three boys, Albert, 11, Theodor, 10, and David, 6 years of age, will in what follows be referred to as Cases 1, 2 and 3, respectively.

These boys, who came under observation two and one-half years ago, during an attack of whooping cough, and who have been under observation ever since, all show an excellent mental development and the two younger ones good physical development. The cyanosis of the skin and mucous membranes is constant and the latter is especially evident in the conjunctival and buccal mucous membranes and in the lips. Their cyanosis increases under various conditions, more especially during periods of excitement following physical overexertion and in the presence of inflammatory conditions of the respiratory tract. The cyanosis decreases on deep voluntary breathing, persisting, however, in the absence of all evidence of bronchial irritation. It differs from the intense blue and purple discoloration, as usually seen in congenital heart cases, and gives the skin a greenish hue, which is especially marked below the eyes and around the nose and mouth, and causes the children to have what might be described as a ghastly appearance.

Case 1.—A boy aged 11 years, with a history of instrumental delivery and a weight of 7 pounds at birth, had been delicate from the beginning. He had his first attack of bronchitis at 1 month with repeated attacks thereafter. His first attack of tonsillitis occurred at the age of 9 months, with subsequent attacks at frequent intervals until his tonsils were removed three years ago. He had pneumonia at 8 years, three months before the cyanosis came on, which was

* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

noted about two and one half years ago, and he had whooping cough in February, 1914. He was intensely cyanotic and appeared desperately ill during the first two weeks of his whooping cough, expectorating much mucus, but not vomiting. A tuberculin skin reaction was first made in 1912 and it was reported as positive. The child is of a nervous temperament. He usually feels well during warm weather, but his bronchitis is aggravated by cold weather and he is generally affected by the cold. He has never had eczema or any other skin lesion.

CASE 2.—A boy, aged 10 years, with a history of having been born at full term, noninstrumental, not asphyxiated at birth, and weighing 7 pounds, has always taken cold easily and suffered from repeated attacks of bronchitis. He had eczema at 2 years of age, lasting six months. He had measles at 6 years, and had two attacks of tonsillitis and severe attacks of whooping cough at the same time as his two brothers. Cyanosis is constantly present and practically the same, although less marked than that of the other boys. He is the most robust of the three boys.

CASE 3.—A boy, aged 6 years, born at full term, noninstrumental, weighing 9 pounds at birth, had repeated attacks of mild bronchitis and had pneumonia when he was 3 years of age. This was followed by whooping cough at the same time his brothers had it. The last disease was very severe and resulted in marked cyanosis, which was constantly present for about 6 weeks. He had a slight attack of eczema, which mainly involved his hands, when he was 4 years old.

A Summary of the Past History.—The three boys were all continuously cyanotic, all of them were subjects to repeated attacks of bronchitis, two of them had had pneumonia, all had had repeated attacks of tonsillitis, all had suffered severely from whooping cough with prolonged increase of their general cyanosis during the first few weeks of the disease, and two of them had had mild eczema.

Family History.—The mother's personal and family history are entirely negative. The father's personal history and his family history, as obtained for three generations, was negative, except for a possible cardiac disease in a brother of the father, who died when he was 4 years of age.

Clinical Examinations.—An examination of the three boys showed that all were exceptionally bright boys. The patient in CASE 1 was delicate and of poor physique, the other two being more robust. Table 1 gives comparative figures as to their general development as compared with boys of similar age.[1]

The cyanosis is more marked in the patients in Cases 1 and 3 than in Case 2 and the latter boy is the best developed physically. It is most marked on the skin of the face, the mucous membrane of mouth, eyes and lips, although the entire body shows more or less cyanosis. There is an absence of clubbing of fingers.

The skin is smooth and soft and presents nothing abnormal, except its color, which is of a greenish hue. The boys were shown before the Western Dermatological Society and the opinion was expressed that the color was not due to a hyperpigmentation of the skin, nor was it thought to be due to any of the various dermatoses, because of the absence of infiltration, hyperkeratosis and scaling. It was thought that the color was subcuticular, the overlying epidermis being perfectly normal, and that the picture presented was not due to a skin condition.

The tuberculin test was positive in Case 1, corroborating the test

1. Whipple, G. M.: Manual of Mental and Physical Tests, Part 1.

TABLE 1.—Development of the Three Boys as Compared with the Normal

	Age, Years	Weight, Lb.	Height, Cm.	Grip Strength, Lb.		Girth Chest, Cm.			Girth 9th Rib, Cm.		Girth Waist, Cm.	Depth Chest, Cm.		Breadth Chest, Cm.	
				R.	L.	Inhal.	Normal	Exhal.	Inhal.	Exhal.		Inhal.	Exhal.	Inhal.	Exhal.
Patient 1.....	11	31.8	136.7	18	17.5	71.1	66.2	64.5	69.8	60.8	63.4	16.6	14.7	22.3	20.2
Average.....	11	32.07	137.19	18.85	17.72										
Patient 2.....	9	23	124.6	13	13.5	64.4	60.8	59.8	62.3	57.2	57.3	15.6	13.3	19.9	18.5
Average.....	9	26.33	126.1	14.34	13.47										
Patient 3.....	5	18.8	110.2	7.5	7.5	58.1	55.2	54.5	57	53.1	54.9	13.8	12	19	17.3
Average.....	5	....	105.9												

made in 1912, and negative in the two younger boys. None of the patients showed any marked glandular enlargement.

Examination of the chest of the boy in Case 1 showed a slight impairment of resonance posteriorly to the left of the spine at the level of the fourth and fifth dorsal vertebrae. Whether this was due to enlarged heart or to peribronchial infiltration was difficult to ascertain. The voice sounds were more distinct over this area and the breath sounds were harsh, with prolonged expiration. Auscultation showed the presence of numerous fine moist râles over both lungs posteriorly on repeated examinations, although not constant. The cardiac area of dulness corresponded with the tele-Roentgen examination. Repeated auscultation of the heart failed to reveal any abnormal findings, except an accentuated second pulmonic sound during the bronchial attacks.

In Case 2 the lungs were negative except for the frequent presence of numerous small, moist râles over both sides posteriorly. There were no abnormal heart sounds and the heart was otherwise negative except for slight enlargement of the cardiac area.

In Case 3 the lung findings were entirely negative except for the frequent presence of fine, moist râles heard over the posterior surface of both lungs.

The roentgenograms in Case 1 showed marked pulmonary findings, indicative of changes in the hilus along the larger trunks of bronchial trees and several areas which might be taken for calcareous deposits. The patient in Case 2 whose picture was taken while he was suffering from severe bronchitis, showed marked infiltration of bronchi, especially of the upper lobes. Case 3 showed very few lung changes.

The Roentgen-ray examination of the heart showed a cardiac enlargement in all three cases, most marked in Case 1. These measurements were made by the tele-Roentgen method, the patient being in the upright position, and were as follows:

HEART DIMENSIONS BY THE TELE-ROENTGEN METHOD, CM.

	Case 1	Normal Children of 131 and 140 cm. Tall (Groedel)
Medium right	3.75	3.08 cm.
Medium left	7	6.79 cm.
Length	11	10.09 cm.

These figures show a diagonal and transverse increase of about 1 cm. over the normal.

HEART DIMENSIONS BY THE TELE-ROENTGEN METHOD. CM.

	Case 3	Normal Children between 102 and 110 cm. Tall (Groedel)
Medium right	3.25	2.55
Medium left	5.5	5.45
Length	9	8.4

Fig. 1.—At 1, 2 and 3 are illustrated the three cyanotic boys, the only children in this family; all show a constant cyanosis of a greenish hue and are without heart murmurs. At 4 is shown a case of congenital heart disease, giving all the typical findings, including a deep purple cyanosis, a loud murmur and clubbed fingers.

These figures show an increase of 0.75 cm. in the transverse diameter and about 0.5 cm. in the oblique length.

In Cases 1 and 2 Roentgen-ray examination shows a marked prominence of the arch of the pulmonary artery and enlargement of the right heart. The latter might be expected in acquired mitral involvement. This can be excluded by the absence of cardiac murmurs.

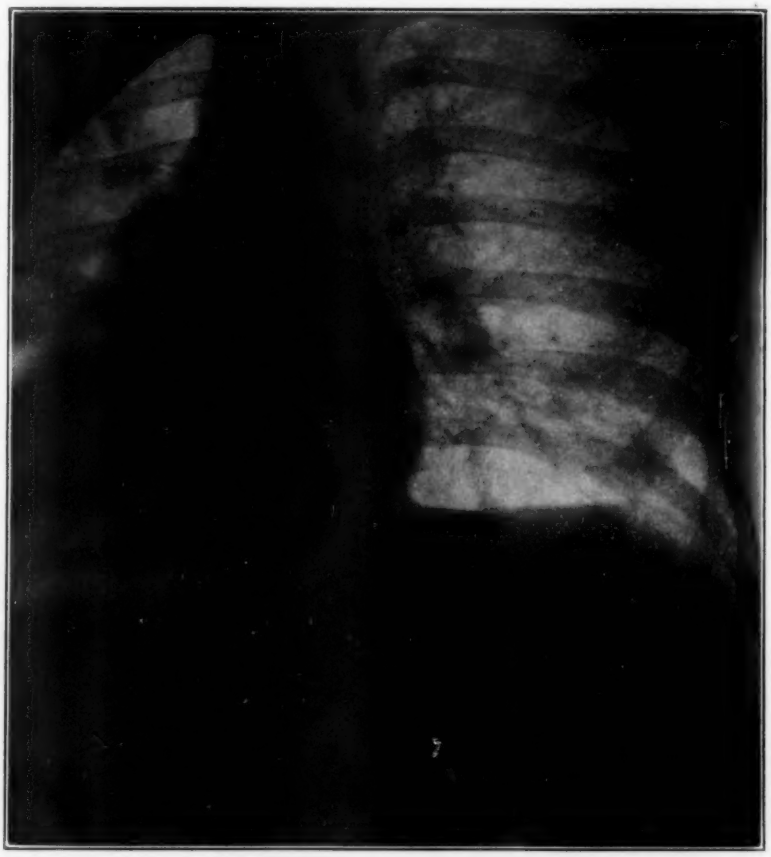

Fig. 2.—Roentgenogram, Case 1.

The pulse and respiration were studied with the polygraph with the following results:

	At Rest		After Severe Exercise	
	Pulse	Respiration	Pulse	Respiration
Case 1	86	24	120	44
Control boy (same size, robust)	80	20	96	27
Case 2	84	24	84	27
			Arrhythmia	
Control boy (frail)	88	22	126	28

In Case 1 and his control it will be noted that both the pulse and respiration rate were higher in the former, and that after severe exercise there was a marked increase in both in Case 1, less so in his control. In Case 2 the control boy had a somewhat higher pulse. This might be accounted for by the fact that he was frail and somewhat anemic. After severe exercise, and this held true for several examinations, neither the pulse nor the respiration rate was noticeably increased in Case 2, but the respirations became deeper and he showed a marked cardiac arrhythmia. His control showed a marked increase in pulse rate, but only a slight increase in the number of respirations. It is difficult to account for the behavior of the pulse and respiration in Case 2 after exercise.

The blood pressure in Cases 1 and 2 and their controls was taken by the auscultatory methods. The following results were obtained:

BLOOD PRESSURE IN CASES 1 AND 2 BY AUSCULTATORY METHOD

	Syst. P.	Diast. P.	Pulse P.	Pulse Rate
Case 1	89	70	19	86
Control	92	66	26	80
Case 2	88	70	18	84
Case 3	70	45	25	84

Judson and Nicholson[2] give the following figures for children of corresponding age, taken by the auscultatory method:

Age, Years	Syst. P.	Diast. P.	Pulse P.	Pulse Rate
11	95.8	62.3	35.5	87
9	91.7	62.2	29.5	84
6	93.8	63.5	30.3	95

It will be noted that in Cases 1 and 2 the pulse pressure was considerably below that of the control and the figures of Judson and Nicholson, showing a lessened peripheral resistance as well as a lessened systolic impulse, as compared with the quoted figures.

The electrocardiograms do not show any great deviation from the normal; however, it will be noted that R is taller in Lead III than in Lead I, while S is deepest in Lead I. This is suggestive of right ventricular hypertrophy. In left ventricular hypertrophy R is usually found tallest in Lead I and shortest in Lead III, while S is deepest in Lead I, the reverse of the above findings. These findings are most marked in Case 2, that of the boy who shows the best general development. In summarizing these findings it may therefore be stated that our electrocardiograms do not vary much from the normal, but indicate a predominance of right-side ventricular activity. Lewis states that if there is one congenital defect in which the electric curves should be normal it is the uncomplicated patency of ductus arteriosus, while marked pulmonary stenosis is usually associated with extreme degrees

2. Judson and Nicholson: AM. JOUR. DIS. CHILD., 1914, **8**, 257.

of right-side hypertrophy, which is amply evidenced in the electrocardiograms, unless decompensation is present.

It was hoped that the blood findings would show some evidence which would aid in the diagnosis. The hemoglobin was examined by spectrophotometer. The Hüfner instrument was used. By this method the absolute number of grams of hemoglobin per 100 c.c. of blood was determined. Case 1 showed 16.33 gm., as compared with the normal 14.57 gm. for his age. Case 2 showed 14.80 gm., and Case 3, 14.45 gm.

Fig. 3.—Roentgenogram, Case 2.

as compared with a normal average of 13.28 gm., showing an absolute increase in the hemoglobin content of the blood.

On spectroscopic examination no band was visible in the red, indicating the absence of appreciable amounts of either methemoglobin or sulphemoglobin. The absorption bands in each of the three cases corresponded to those of oxy-hemoglobin. This would exclude enterogenous cyanosis from further consideration. The examinations were made with Krüss spectroscopic apparatus. Several cubic centimeters of blood were removed from a vein by means of a syringe and placed into twice the volume of distilled water. The solution was then filtered.

The filtrate was placed into a cell for observation of the absorption bands in the spectroscope. Distilled water was added until good transmission of only the red light was obtained. The addition of phenylhydrazin, which has a tendency to intensify the sulphemoglobin band in the red, failed to bring out any such band in these solutions.

The resistance of the red blood corpuscles was tested by a slight modification of that of Limbeck and Hamburger. Small amounts of the washed corpuscles are placed in varying concentrations of sodium chlorid solution from 0.3 per cent. to 0.75 per cent., incubated for two hours and then the beginning and end points of hemolysis read. The figures were well within the normal limits; that of Case 1 beginning at 0.375 per cent. and completed at 0.325; Case 2 beginning at 0.4

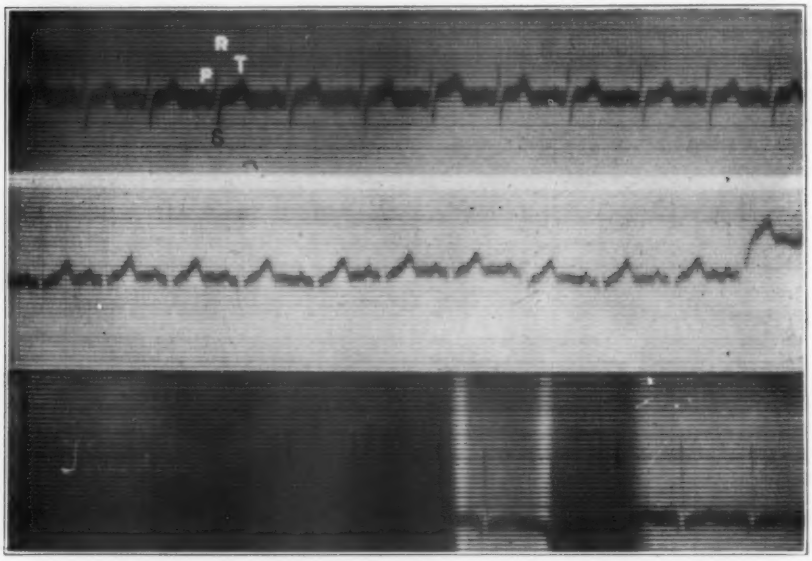

Fig. 4.—Electrocardiograms taken in Case 2. Upper, Lead I; middle, Lead II; lower, Lead III.

and complete at 0.325, and Case 3 beginning at 0.4 and complete at 0.35.

The Duboscq colorimeter failed to show any abnormal pigment in the plasma when compared to normal plasma.

Further examination of the blood showed the following:

	Case 1	Case 2	Case 3
Erythrocytes	3,900,000	4,280,000	4,100,000
Leukocytes	6,800	12,400	12,900
Differential	Per Cent.	Per Cent.	Per Cent.
Lymphocytes	42	34	39
Large Mononuclears	3	1	4
Neutrophils	50	61	52
Transitionals	1	2	2
Eosinophils	2	2	3
Basophils	2		

The red cells showed no degenerative changes, were about normal in number and shape, somewhat enlarged, were deeply colored, contained an excessive amount of hemoglobin, as shown by the spectrophotometer, and their resistance was normal. The white cells showed comparatively normal average and total count in Cases 2 and 3, somewhat less so in Case 1. This upholds the idea that there is absence of blood concentration. The differential counts were normal in Cases 2 and 3 with a somewhat higher lymphocyte count in Case 1; the total leukocyte count and high lymphocyte percentage in Case 1 may have a relationship to the positive tuberculin reaction in this case.

The temperature of the boys averaged about 37.4 C.

The liver at no time showed evidence of any marked degree of enlargement. This holds true during the repeated attacks of bronchitis and during the whooping cough.

The spleen was never palpable in any of the cases.

The urine was always negative to tests for albumin, sugar, and acetone and never contained more than traces of indican. Blood, pus and casts were never found.

The feces showed a normal bacterial flora and an absence of parasites. At no time was there a protracted constipation.

Impaired circulation through the tissues might account for the cyanosis. Therefore we measured the volume of blood flow through the hands by the Stewart method. His method depends on the principle that the heat given off by the hand at rest is derived entirely from the circulating blood. Knowing the temperature of the arterial blood, the temperature of venous blood and the number of calories given off in a given time, we can calculate the amount of blood that must have flowed in a given area. By this method it was determined that in Case 1 there was a blood flow of 10.9 c.c. a minute per 100 gm. of hand, a figure well within normal limits and almost twice as high as was obtained at the same time under the same conditions from a healthy boy of the same age. Normal figures for the adult, as quoted by Lowey and Schröter,[3] are 6.4 c.c. per 100 gm. per minute; according to Pletsch[4] 3.9 to 8.8 c.c. per minute, the average being 6.12 c.c. per minute; according to Hewlett[5] and his co-workers between 2 c.c. and 8 c.c. per 100 gm. per minute, and according to Stewart[6] 3.5 c.c. to 14 c.c. per 100 gm. per minute.

The slight differences from the normal heart rate and systolic pressure are not sufficient to explain the cyanosis, even in the presence of a lessened pulse pressure in Cases 1 and 2.

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3. Lowey and Schröter: Ztschr. f. exper. Path. u. Therap., 1905, **1,** 197.
4. Plesch: Ztschr. f. exper. Path. u. Therap., 1909, **6,** 462.
5. Hewlett: Am. Jour. Med. Sci., 1913, **145,** 656.
6. Stewart: Harvey Lecture, Nov. 23, 1912.

The failure to find on physical examination abnormalities sufficient to make a positive diagnosis of an abnormal circulation led us to seek for a possible change in the chemical composition of the blood. With the exception of a high hemoglobin content, the blood was normal to the ordinary tests. Spectrophotometric examination of the blood showed no alteration in the nature of the hemoglobin. The plasma was not discolored, and the available alkalinity of the blood as determined by the method of Van Slyke gave the same figure as for children of the same age.

In order to determine whether or not there was a change in the respiratory function of the lungs or tissues, which either prevent the blood from taking up oxygen in the lungs or else more completely depleted it of its supply in the tissues (either condition leading to decrease in the oxygen content of the blood), an examination of the respiratory exchange was made in Case 1 and in his control of the same age during a period of rest and the results obtained are shown in the following tabulation:

COMPARISON OF THE RESPIRATORY EXCHANGE OF THE BOY IN CASE 1 AND HIS CONTROL (NORMAL)

	Weight, Kg.	Expired air at 760 Mm. Hg. and OC., C.c.	%CO_2	CO_2 per Minute, C.c.	CO_2 per Kg. Body Weight per Min., C.c.
Case 1	32.2	2970	2.70	80	2.43
Control (normal)	37.2	2540	3.81	96.8	2.69

These results show that the cyanotic boy inspired 20 per cent. more air per minute than the normal control. However the percentage of carbon dioxid in the expired air was about 25 per cent. less, thus making the total carbon dioxid excreted per minute, when reduced to cubic centimeter excreted per kilogram body weight, practically the same in both boys. These results definitely show that the abnormality is not metabolic, and that it lies in a deficient aeration of the blood which is sent into the systemic circulation.

In the hopes that figures might be obtained which would throw light on the condition, the following experiments were made, the object of which was to determine the difference in the amount of carbon dioxid found in the arterial and the venous blood in the case of the cyanotic and the normal boy. In order to determine the change which the blood undergoes in the lesser circulation, it was necessary to compare the blood from the right with that from the left side of the heart, an operation which was practically impossible. It was therefore necessary to find other methods for estimating the amount of carbon dioxid in the venous blood. This is possible, as has been shown by Christiansen, Douglas and Haldane,[7] who have devised a method for obtaining

7. Christiansen, J., Douglas, C. G., and Haldane, J. S.: Carbon Dioxid in the Blood, Jour. Physiol., 1914, **48**, 244.

the tension of the carbon dioxid in the venous blood. Their method consists in having the patient inspire and expire air from a spirometer, this air containing known percentage of carbon dioxid, and then estimating the carbon dioxid content of that air at the end of eight and thirteen seconds of breathing into the spirometer. As the time of the lesser circulation is somewhat greater than thirteen seconds, the air in the bag is only in contact with venous blood. Repeated tests were made, beginning with air containing approximately the amount of carbon dioxid contained in alveolar air, and again with air containing about 2 per cent. more than alveolar air. When, after repeating the test with the different percentages of carbon dioxid in the rubber bag, the point is reached at which no change takes place in the percentage composition of the test air between the eighth and the thirteenth second of breathing, the tension of carbon dioxid in the spirometer at this point equals the tension of the carbon dioxid in the venous blood. The tension of carbon dioxid in the arterial blood is that found by obtaining the percentage of carbon dioxid in the alveolar air, which is estimated by the method of Haldane.[8] This consists in estimating the percentage of carbon dioxid in the last portion of the expired air of a forcible expiration, and then determining the partial pressure of the gas at the barometric pressure and temperature at which the analysis was made. [Per cent. of carbon dioxid $\times$ (barometric pressure — vapor tensions at temperature of analysis = tension of carbon dioxid in the blood.]

Correcting the difference in the tensions between arterial and venous bloods on the basis of the influence which the oxygen concentration has on carbon dioxid tension[7] and then consulting the absorption curve of blood at the tensions of the arterial carbon dioxid and the corrected tension of venous carbon dioxid, the amount of carbon dioxid which each holds is read off. From the difference in the amount of carbon dioxid held in the arterial and in the venous blood thus determined, the amount of carbon dioxid each cubic centimeter of blood loses on passing through the lungs may be calculated. A tabulation of the results of these experiments is shown in Table 2.

Knowing the number of cubic centimeters of carbon dioxid excreted per minute and the amount of carbon dioxid in a definite amount of blood passing through the lungs, we can determine by calculation the number of cubic centimeters of blood passing through the lungs per unit of time, this latter being illustrated by quoting the following experiment made on our boys:

In Case 1 the alveolar carbon dioxid tension (Table 2) was about 35.1 mm. of mercury and the venous carbon dioxid tension was 48.9

8. Haldane: Method of Air Analysis, London, 1912.

mm. of mercury. This gives a difference of 13.8 mm. of mercury pressure of carbón dioxid between venous and arterial blood. In the case of the normal control boy the alveolar carbon dioxid was 39.6 mm. and the venous carbon dioxid was 45.4. This gives a difference of 5.8 mm. of mercury pressure of carbon dioxid between venous and arterial blood, the latter being the average normal figures as shown by Christiansen, Douglas and Haldane,[9] who give from 6.3 to 6.9 for adults. In other words, the difference between the tension of carbon dioxid in arterial and in venous blood is 170 per cent. greater in Case 1 than in the normal control. In Case 2 the difference is only 21 per cent. between the patient and the normal control, who unfortunately gave a difference between arterial and venous carbon dioxid tension a little

TABLE 2.—VARIATION IN CARBON DIOXID PRESSURE IN EQUILIBRIUM WITH THE BLOOD ENTERING AND LEAVING THE LUNGS (VENOUS AND ARTERIAL BLOOD) IN THE CASE OF THE NORMAL AND CYANOTIC BOYS

	Age, Years	Weight, Kg.	Date	Mm. Hg CO_2 Pressure		Difference Mm. Hg	Average Difference, Mm. Hg	Per Cent. Diff.
				Arterial Blood	Venous Blood			
Case 1	11	32.3	5/27	35.1	48.9	13.8		
			5/31	34.5	48.1	13.6		
			6/ 1	36	—	—		
			6/ 3	35.5	47.6	14.1	13.8	
Control (normal)	.1	37.2	5/27	39.08	45.4	6.32		
			6/ 1	39.6	45.6	6	....	170
			6/ 3	39.1	44.1	5.1	5.8	
Case 2	9	23.2	6/ 1	33.4	42.3	8.9		
			6/ 3	31.8	40.2	8.4	8.7	
Control (normal)	10½	22.7	6/ 1	32.4	39.1	6.7		
			6/ 3	32.3	40	7.7	7.2	21

greater than one would expect in a normal case, probably because of our inability to obtain a fair sample of alveolar air from him.

On reducing these figures into cubic centimeters of blood flowing through the lungs per minute or per heart beat the difference is unexpectedly great (Table 3).

The normal boy has a ventricular output of 38.4 c.c. per heart beat, which is about what we would expect from the available data of other observers, whereas in Case 1 the boy has only 13.9 c.c. per heart beat passing through his lungs. But each 100 c.c. of blood of the boy in Case 1 loses about 7 c.c. of carbon dioxid in comparison to 3 c.c. lost by 100 c.c. in the normal control's blood passing through the lungs. In other words, the effect of the reduced blood flow through the lungs

9. Christiansen, J., Douglas, C. G., and Haldane, J. S.: Carbon Dioxid in the Blood, Jour. Physiol., 1914, **48**, 268.

in the case of the cyanotic boys is compensated somewhat by its carrying an increased load of carbon dioxid per cubic centimeter, which the blood brings up to the lungs and also by the increased amount of oxygen which the blood carries per cubic centimeter to the heart, in virtue of its increased hemoglobin contents.

The results of these analyses show that the cyanosis is not a faulty gas exchange of the blood as it passes through the lungs, for this is above normal, but rather lies in a reduction of the amount of blood which reaches the left ventricle from the pulmonary circulation. The rate of blood flow is normal or above normal through the systemic circulation. We are therefore forced to believe that the blood sent from the left ventricle is a mixture of venous and arterial blood, and that the tension of oxygen in the arterial blood is below that normally found. The larger percentage of reduced hemoglobin in their arterial

TABLE 3.—Relative Amount of Blood Flowing into the Lungs at Each Heart Beat, as Computed from Available Data

	Albert (Blue)	Bert (Normal)
Cc. CO_2 contained in 100 c.c. of blood at average mm. Hg. pressure in arterial blood	50.5	53
C.c. CO_2 contained in 100 c.c. of blood at average mm. Hg. CO_2 pressure in venous blood.	57.5	56
C.c. CO_2 lost by 100 c.c. of blood in passing through the lungs	7	3
C.c. CO_2 excreted per minute	80	96.8
Blood flow per minute through lungs	1140 c.c.	3230 c.c.
Pulse rate	82	80
C.c. blood delivered into lungs at each heart beat	13.9	40.4

blood than is found in normal individuals imparts the blue color to their skin. The amount of oxygen, however, delivered to the tissues is sufficient to meet their needs, due at least in part to the increased hemoglobin content of the blood; and the amount of carbon dioxid excreted by their lungs is kept within normal limits by the greater difference in the effectual diffusion pressure of carbon dioxid between arterial and venous blood in the lungs.

The cyanotic boys are not different from other boys in their ability to do the ordinary things of life. However, their power of endurance does not compare with that of a normal boy. When forced pulmonary ventilation is pushed, the color markedly improves. Albert can hold his breath as long as a normal boy, but he cannot stand the muscular exertion that a normal boy can. These boys are all subject to bronchitis and this tendency might be explained on the assumption that a deficient oxygen supply in the blood of the bronchial artery is a factor in producing congestion or edema in the lungs, as suggested by Martin Fisher.[10]

10. Fisher, Martin: Edema, John Wiley & Sons, New York, 1910.

We are led, therefore, to conclude that the pathology consists of a cardiac abnormality, basing our conclusions on the result of our studies of the respiratory exchange and corroborated by the clinical studies, as shown by the electrocardiograms and radiograms.

The methods, as outlined here, afford a new means of investigating the relationship of the pulmonic circulation to the systemic circulation, and in the present case renders the diagnosis of a septal or ductus defect highly probable.

This work is being carried on at present in the laboratory of physiology in the University of Illinois, and the laboratory of pathology of the Cook County Hospital.

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THE PHENOL EXCRETION IN THE URINE OF INFANTS, INCLUDING THE NEW-BORN *

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Phenol was first found in normal urine by von Städeler[1] in 1851. Since his day the phenols isolated from urine are phenol, paracresol, orthrocresol, pyrocatechin, hydroquinone, and para-oxybenzoic acid. The most important of these, according to Baumann,[2] Mooser,[3] and Siegfried and Zimmermann,[4] is paracresol.

Städeler tested the urine distillate qualitatively with Millon's reagent. Baumann used a gravimetric method in which he converted the phenol into crystals of tribromphenol. The first volumetric method was originated by Messinger and Vortman. This was modified by Kossler and Penny,[5] and later by Neuberg,[6] Mooser,[3] Siegfried and Zimmerman,[7] and finally by Ellinger and Henzel.[8] Among the colorimetric methods worthy of notice are those of Bananni,[9] Bordas and Bobin,[9] and Kiesel.[9] It remained, however, for Folin and Denis to devise a method which was both accurate and clinically applicable.

In 1879 H. Senator,[10] using a qualitative test for phenol, found volatile (*flüchtige*) traces of it in the urines of two infants. Three others gave negative results. Ludwig F. Meyer[11] in 1905, using the

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1. Von Städeler, G.: Ann. d. Chem. u. Pharm., 1851, **77,** 17; cited from Baumann, E.: Ueber Gepaarte Schwefelsaüren im Organismus, Arch. f. Physiol., 1876, **13,** 287.

2. Baumann, E.: Ueber den Nachweis und die Darstellung von Phenolen und Oxysäuren aus dem Harn, Ztschr. f. physiol. Chem., 1882, **6,** 183.

3. Mooser, W.: Beitrag zur Kenntnis der aromatishchen Körper des Harns, Ztschr. f. physiol. Chem., 1909, **63,** 155.

4. Siegfried, M., and Zimmerman, R.: Die getrennte Bestimmung von Phenol and Parakresol im Harns, Biochem. Ztschr., 1911, **34,** 462.

5. Kossler, A. V., and Penny, E.: Ueber die massanalytische Bestimmung der Phenols im Harn, Ztschr. f. physiol. Chem., 1893, **17,** 117.

6. Neuberg, C.: Ueber die quantitative Bestimmung des Phenols im Harn, Ztschr. f. physiol. Chem., 1899, **27,** 123.

7. Neubauer and Huppert: Analyse des Harns, 1913, **2,** 788.

8. Hensel, Marie: Zur Methodik der Phenolbestimmung im Harn, Ztschr. f. physiol. Chem., 1912, **78,** 373.

9. Neubauer and Huppert: Analyse des Harns, 1913, **2,** 793.

10. Senator, H.: Ueber das Vorkommen von Produktion der Darmfaulniss bei Neugeborenen, Ztschr. f. physiol. Chem., 1880, **4,** 1.

11. Meyer, Ludwig F.: Zur Kenntnis der Phenolausscheidung beim Zäugling. Monatsch. f. Kinderh., 1905, **4,** 344.

method of Kossler and Penny, investigated the phenol excretion of seven infants and found it present in every case.

At the instigation of Dr. Otto Folin a study of the urinary excretion of phenol in normal infants was undertaken. Later, in reviewing the literature, it was found that there were no data relative to quantitative determinations on the phenol excreted by the new-born. Dr. J. P. Sedgwick, therefore, suggested that the new-born be included in this investigation.

The Folin and Denis[12] method was used with a slight modification which insures more uniform results in cold weather and gives the maximum blue color in a shorter time. In transferring the solutions to be tested for total phenol from the large test tubes to volumetric flasks, as Folin directs, the amounts of rinse water used often varied, hence the amounts of lukewarm water required in filling to volume varied accordingly. Consequently some flasks would be cooler than others. A cool flask often did not reach its maximum color for an hour or more. In this, as in most other colorimetric work, uniformity in temperature is essential to uniformity in depth of color. To avoid delay the technic was modified as follows: all flasks, after being filled to volume, were placed in a water-bath with a temperature of from 40 to 45 C. In about ten minutes all were ready for the colorimeter.

In measuring 20 c.c. of the second filtrate to be used in testing for free and for total phenol, the same pipet was used for both to insure equal volumes. Both the free and the total phenol of each specimen were read against the same standard.

In using the large test tubes placed within a tall 600 c.c. beaker, as Folin and Denis direct, it was found more satisfactory to use a wire gauze so arranged in the beaker as to support the test tubes about 3 cm. from the bottom. The top of each test tube then extends over the side of the beaker, and assisted by the contained funnel, it becomes a perfect condenser, provided the water is not boiled too vigorously. Instead of heating the test tubes over a free flame, it was found preferable to place them directly into the boiling water-bath for one minute. After this a microburner was used and the water kept hot, but not boiling, for ten minutes.

In testing known solutions of phenol, the results with a funnel condenser were compared with those obtained with a reflux condenser. When used as described above, the funnel condenser is absolutely accurate, that is, no phenol is lost by evaporation.

Folin and Denis found some cases in which the free phenol constituted 100 per cent. of the total phenol. In our cases, with the technic

12. Folin, O., and Denis, W.: A Colorimetric Method for the Determination of Phenols (and Phenol Derivatives) in Urine, Jour. Biol. Chem., 1915, **22,** 305.

as described above, some combined phenol was always present. Also our average percentage of combined phenol was greater than theirs.

The specific gravity of infants' urine is usually 1.005 to 1.010. With such dilute urine, 20 to 25 c.c. are necessary for a test and 40 c.c. of the first filtrate are most convenient. The specific gravity of the urine of the new-born is from 1.020 to 1.030. With them 5 c.c. give the most satisfactory results and only 25 c.c. of the first filtrate are necessary.

The number of infants whose urine was studied was fifteen. With several, the urine was tested daily for three successive weeks, during which time week-end rest periods of three days each were allowed. A total of ninety-five twenty-four hour specimens were examined. The number of new-born infants whose urine was studied was nineteen. Each specimen included the urine passed during the first three days of life. In studying these 114 specimens a total of 164 analyses were made. Where two or more analyses were made on the same specimen the average only is given.

Table 1 gives the principal points needed for a metabolic study of these fifteen infants, including age, weight, sex, clinical condition, amount and kind of diet, number and consistence of stools and, in addition, the urinary record. None of these cases had hyperpyrexia at any time and the records of temperature were therefore omitted.

The diets in numbers from 4 to 12, inclusive, were prepared in the Walker-Gordon laboratory in Boston. In those cases in which homogenized milk was given the proportions of the food elements were estimated with great accuracy.

The results from the homogenizing of whole milk or of olive oil mixed with fat-free milk show no effect on the phenol excretion. This was to be expected, since it has long been established that phenols arise from proteins.

The ages of these infants varied from 1 week to 6 months, their weights varied from 1,765 gm. to 5,740 gm., the food intake from 405 to 1,080 gm. and the number of stools per day from one to nine.

The total phenol excretion per day ranged from 9 mg. in Case 14 to 58 mg. in Case 4. The average phenol excretion per day was 28.9 mg., of which 83 per cent. was free phenol.

The consistence of the stools in these cases was apparently not a determining factor in the amount of phenol excreted. This agrees with observations of Meyer[11] and with the statement of Freund[13] with reference to the output of ethereal sulphates.

For the sake of ready comparison, I have tabulated the data given by Meyer on his cases and present it in Table 2. In these cases the

13. Freund, W.: Zur Kenntniss der Schwefelausscheidung bei Säuglingen. Ztschr. f. physiol. Chem., 1900, **29,** 5, 24.

TABLE 1.—URINARY RECORD AND OTHER—

No.	Name	Sex	Age	Clinical Condition	Weight with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
4	Lamachia..	♂	3 mo.	Under nourished...	4,300	1,050 c.c. modified milk..	2.5	6	1.25
						Average.....	...	...	....
5	Casey.....	♂	6 mo.	Healthy.....	3,550	1,050 c.c. modified milk..	1	5.6	1.5
						Average.....	...	...	....
6	Walsh.....	♂	6 mo.	Healthy.....	5,340	1,050 c.c. modified milk..	2	6	1.75
					—60	Average for week.....	...	...	....
					5,260	1,050 c.c. modified milk.. homogenized	2	6	1.75
					No change	Average for week.....	...	...	....
					5,260	1,050 c.c. special homogenized [the 2 % fat is olive oil]	2	6	1.75
					—180	Average for week.....	...	...	....
						Avg. 22 determinations.	...	...	....

—Data of the Author's Fifteen Cases

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
...	....	780	.....	2.36	54.2	61.5	88	12
		630	.....	3.42	43.1	54.6	79	21
...	....	705	.....	2.89	48.6	58	83	17
...	....	750	.....	1.16	40.4	42.6	94	6
		600	.....	1.01	39.6	43.3	91	9
		930	.....	1.62	72.7	80.6	90	10
...	....	726	.....	1.26	50.9	55.8	91	9
3	△	855	.....	....	29.2	35.3	80	20
1	△	780	.....	....	25.7	31.2	80	20
1	△	840	.....	....	34.8	36.2	96	4
3	○	720	.....	....	25.6	30.6	83	17
3	○	780	.....	....	34.4	40.9	84	16
2	△	740	.....	....	37.1	39.6	93	7
1	△	825	.....	....	28.4	39.3	72	28
2	....	790	.....	2.191	30.6	35.6	86	14
3	—	780	1.008	1.394	21.6	26.2	83	17
4	△	810	1.010	1.11	23.4	27.4	86	14
2	△	750	1.009	1.471	30.6	33.3	92	8
3	△	810	1.007	2.002	27.6	32.9	80	20
		810	1.008	1.929	31.6	34.9	90	10
5	△	660	1.011	1.788	21.4	30	70	30
3	△	705	1.009	1.659	28.6	32.3	88	12
2	△	780	1.005	1.954	24.8	32.5	66	34
3	....	763	1.007	1.65	26.2	31.2	84	16
2	△	870	1.011	2.179	30.2	39.9	76	24
2	△	750	1.011	1.488	27.9	32.3	86	14
1	△	840	1.012	1.835	17.9	22	81	19
1	—	810	1.008	1.053	17	25.3	67	33
1	△	840	1.006	2.151	19.5	29	67	33
1	△	840	1.012	2.141	19.7	29.6	67	33
1	△	780	1.012	1.945	15.4	24.7	62	38
1.3	....	790	1.010	1.912	20.7	29.1	65	35
2	....	761	.....	1.917	25.8	30.9	83	17

TABLE 1.—URINARY RECORD AND OTHER DATA—

No.	Name	Sex	Age	Clinical Condition	Weight, with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
7	Reddish....	♀	2 mo.	Normal.....	3,095	630 c.c. breast milk....	4	7	1.5
					+270	Average for week.....	...	...	....
					3,265	630 c.c. breast milk; homogenized	4	7	1.5
					+90	Average for week.....	...	...	....
					3,350	630 c.c. breast milk....	4	7	1.5
					+30	Average for week.....	...	...	....
						Avg. 19 determinations.	...	...	....
8	Zuealla.....	♂	4 mo.	Balance disturbance	3,265	945 c.c. special homogenized [Olive oil 1.6 %]	1.6	6	1.28
					−90	Average for week.....	...	...	....
					3,890	945 c.c. modified milk..	1.6	6	1.28
					−120	Average for week.....	...	...	....
					3,835	945 c.c. modified milk; homogenized	1.6	6	1.28
					+30	Average for week.....	...	...	....
						Avg. 11 determinations.	...	...	....

—OF THE AUTHOR'S FIFTEEN CASES—(*Continued*)

Stools		Urine			Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
...	△	480	1.004	0.318	10	13.2	75	25
	△	480	1.004	0.586	9.6	11.2	85	15
8	—	465	1.005	0.895	15	17.6	85	15
5	—	465	1.006	0.65	8.1	15.3	53	47
4	—	465	.....	0.706	9.3	11	84	16
6	—	420	.....	0.513	8.4	12	70	30
5	—	480	1.010	0.524	9.2	11.4	80	20
6	—	450	1.010	0.575	9	11.8	76	24
2	—	420	.....	0.501	10	11.8	85	15
5.1	....	458	1.006	0.585	9.8	12.8	76	23
8	△	390	1.008	0.459	10.3	12.5	80	20
4	—	420	1.008	0.513	15.2	17	89	11
2	—	330	.....	0.4	7.9	12.1	65	35
5	—	360	.....	0.437	8.3	10.4	80	20
3	—	420	.....	0.464	9.6	13.9	79	21
3	—	390	.....	0.387	8.1	11	74	26
4.2	....	385	1.008	0.285	10.1	12.8	79	21
5	—	420	1.008	0.518	12.2	15.7	78	22
6	△	300	.....	0.195	7.6	10.1	75	25
3	△	360	1.006	0.464	8.8	12.3	78	22
2	—	390	1.006	0.453	7.5	9.9	75	25
4	....	417	1.007	0.407	9	12	75	25
5+	....	420	.....	0.426	9.7	12.6	77	23
2	—	780	1.010	1.355	19	23.9	80	20
6	—	840	1.008	1.083	24.3	32.8	74	26
4	△	840	1.010	1.072	22.2	31.9	70	30
4	....	820	1.009	1.17	21.8	29.5	74	26
3	○	810	1.010	1.593	35.8	47.2	78	22
1	△	600	1.012	1.239	26.6	36.1	73	27
2	○	720	1.008	1.481	35.2	42.2	83	17
2	....	710	1.007	1.437	32.5	41.8	78	22
6	—	630	1.012	1.471	21.9	23.9	90	10
9	—	390	.....	.....	17.4	20	87	13
6	—	570	1.010	1.257	17	24.2	70	30
4	△	600	1.010	1.244	12.1	17.4	69	31
2	△	630	1.011	1.339	13.3	25.9	55	45
5.5	....	560	1.010	1.303	16.3	22.3	77	23
4	....	698	1.009	1.303	23.5	31.2	76	23

TABLE 1.—URINARY RECORD AND OTHER DATA—

No.	Name	Sex	Age	Clinical Condition	Weight, with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
9	Adams.....	♀	4 mo.	Normal.....	4,290	960 c.c. special homogenized [Olive oil 2%; barley starch 0.75%]	2	6	1.6
					+60	Average for week.....	...	...	....
					4,430	960 c.c. modified milk.. [Barley starch 0.75%]	2	6	1.6
					+120	Average for week.....	...	...	....
					4,430	960 c.c. modified milk.. [Barley starch 0.75%]	2	6	1.6
					+60	Average for week.....	...	...	....
						Avg. 11 determinations.	...	...	....
10	Caples.....	♂	6 mo.	Acute intestinal	5,340	1,080 c.c. modified milk.. [Barley starch 0.75%]	2	6	1.75
					No change	Average.....	...	...	....
11	Gilman.....	♂	5 wk.	Malnutrition.....	1,765	750 c.c. breast milk, 8 parts; whey, 2 parts; lactose to 6%	3.2	6	1.4
					+90	Average.....	...	...	....
12	Crowley....	♂	2 mo.	"Colic"; well nourished	4,680	735 c.c. modified milk.. [Barley starch 0.75%]	2.4	6	1.9
					+90	Average for week.....	...	...	....

—OF THE AUTHOR'S FIFTEEN CASES—(*Continued*)

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
4	—	750	1.010	1.414	32.3	40.4	80	20
2	△	720	1.012	1.415	32.2	37.2	86	14
4	△	750	1.010	1.618	34.2	39.8	86	14
3.3	....	740	1.010	1.482	32.9	39.1	84	16
7	△	510	1.009	1.484	22.9	26.6	86	14
8	—	600	1.010	1.999	28.2	31.3	90	10
4	—	375	1.012	1.187	18.7	23.5	79	21
6.3	....	495	1.010	1.557	23.3	27.1	86	14
6	—	570	.....	1.482	28.5	31	92	8
4	—	510	.....	1.532	17.5	20.4	86	14
1	—	570	.....	1.48	15.5	18.7	83	17
4	△	615	1.010	1.547	16	25.6	62	38
3	△	630	1.012	1.663	26.3	29.2	83	17
3.6	....	579	1.011	1.541	20.7	24.9	84	16
4.3	....	605	1.010	1.526	25.6	30.3	85	15
6	—	780	1.010	1.171	16.6	25.1	66	34
8	△	840	.....	1.864	18.4	26.6	69	31
9	—	720	1.010	1.501	14.3	20	72	28
5	—	855	.....	1.557	21.1	24.3	87	13
7	....	799	1.010	1.523	17.6	24	73	27
8	—	420	1.004	0.198	7	9	67	33
5	—	450	1.005	0.26	8.7	11.4	76	24
10	—	570	1.005	0.279	8.9	10.6	84	16
4	—	420	1.008	0.391	10.8	11.2	96	4
7	....	465	1.006	0.382	8.8	10.5	83	17
2	△	450	1.010	1.236	19.5	24.2	80	20
3	△	690	1.012	2.019	22.5	30	75	25
3	△	660	1.010	1.926	13.8	20.1	68	32
4	△	690	1.014	2.618	13.5	16.4	80	20
3	....	622	1.011	1.975	17.3	22.7	77	23

TABLE 1.—URINARY RECORD AND OTHER DATA—

No.	Name	Sex	Age	Clinical Condition	Weight, with Gain or Loss for Week, Gm.	Diet			
						Amount and Kind	Per Cent. Fat	Per Cent. Carbohyd.	Per Cent. Protein
12 Cont.	Crowley....	♂	2 mo.	"Colic"; well nourished	4,770	735 c.c. special homogenized [Olive oil 2.4%; barley starch 0.30%]	2.4	6	1.9
					—60	Average for week.....	...	...	....
						Avg. 9 determinations..	...	...	....
13	Glover.....	♂	2 wk.	Normal.....	2,860	Breast fed, 5 feedings...	...	...	....
						[Amount not recorded]			
					+40	Average for week.....	...	...	....
14*	Vincent....	♂	1 wk.	Normal.....	2,860	Breast fed, 5 feedings...	...	...	....
						[Amount not recorded]			
					+80	Average for week.....	...	...	....
18	Packer.....	♂	3 mo.	Normal; undernourished	3,600	750 c.c. protein milk + 7% dextrimaltose	...	...	....
					+120	Average for week.....	...	...	....
20	Tollefson..	♂	6 mo.	Cleft palate; otitis media	4,950	750 c.c. ½ milk, ½ oatmeal water + 4% sugar; cereal b.i.d.	...	...	....
					—50	Average for week.....	...	...	....
21	Samuelson	..	6 wk.	Healthy.....	5,740	960 gm. breast milk.....	...	...	....
					+210	Average for week.....	...	...	....
22	Voulas....	..	9 wk.	Healthy.....	2,840 —70	405 gm. breast milk.....	...	...	....
						General average of the 15 cases.....			

* A 72-hour specimen.

—OF THE AUTHOR'S FIFTEEN CASES—(*Continued*)

Stools		Urine						
					Phenol			
Number	Form	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
4	△	525	.....	1.162	14.9	17.3	85	15
4	△	630	1.012	1.741	18.8	19.2	97	3
4	△	600	1.010	1.578	....	25.9	..	..
3	△	480	1.012	1.334	13.3	20	66	34
4	—	480	1.014	1.465	14.3	23	67	33
4	....	543	1.012	1.465	15.3	21.1	73	27
3.5	....	583	1.011	1.686	16.3	21.9	75	25
1	△	120	1.006	0.265	8.6	11.1	77	23
1	△	180	.....	0.264	15.6	16.1	97	3
...	....	150	1.006	0.264	12.1	13.6	89	11
2	△	...	.....	.....	....	....	..	..
1	△	...	.....	.....	....	....	..	..
1	△	100	1.022	0.88	22.6	27.1	83	17
...	....	34	.....	0.293	7.5	9	83	17
1	□	250	1.012	1.1	14.9	17.3	87	13
2	△	200	1.008	1.27	15.3	16.7	92	8
...	....	225	1.010	1.185	15.1	17	89	11
1	△	240	1.010	0.947	24	27.5	87	13
1	△	180	1.014	1.436	37.7	40.1	94	6
...	....	210	1.012	1.192	30.8	33.8	91	9
2	△	425	1.010	0.509	28.7	38.3	75	25
2	△	380	1.006	0.316	28.4	35.2	81	19
...	....	402	.....	0.412	28.5	36.7	78	22
2	○	155	1.007	0.358	18.6	21.6	87	13
...	....	463	.....	1.107	24	28.9	83	17

Characters indicating consistency of stools are as follows: ○, formed; △, intermediate or soft; —, watery; □, soap stool.

phenol excretion varies from 2.5 to 16.9 mg., the average for his breast-fed infants being 4.19 mg. and for the artificially fed infants 13.28 mg. He does not state the daily output of urine or the total nitrogen. These figures of Meyer constitute the only quantitative investigations made on infants previous to 1915 found in a thorough review of the literature.

TABLE 2.—DATA DERIVED FROM L. F. MEYER'S CASES

No.	Age	Weight, Gm.	Clinical Condition	Diet	Stools	Phenol, Mg.
1	6 mo.	6,330	Healthy.....	850 gm. breast milk	.....	5.87
2	10 wk.	.....	Healthy.....	600 gm. breast milk*	.....	2.507
3	7 wk.	3,450	Healthy.....	Condensed milk "Schleim" and sugar	3 yellow, thin	8.46
4	5¾ mo.	4,350	Healthy.....	Solution of powdered milk	3 yellow, thin	12.22
5	13 mo.	5,740	Very rachitic.....	600 gm., ½ milk, ½ flour and gruel soup	3 yellow, thin	13.16
6	4¼ mo.	4,000	.....	½ flour soup, ½ powdered milk solution	4 yellow, thin	15.67
7	10 mo.	5,020	Underdeveloped, rachitic, perspiring greatly	Breast milk and buttermilk†	1 yellow, homogeneous	16.92

* Average in breast-fed infants 4.19.
† Average in artificially-fed infants 13.28.

TABLE 3.—PHENOL EXCRETION IN URINE OF HOSPITAL INFANTS (FOLIN AND DENIS)

No.	Age, Mo.	Clinical Condition	Volume, C.c.	Total N, Gm.	Phenol			
					Free, Mg.	Total, Mg.	Free, per Cent.	Conjugated, per Cent.
61	10	Malnutrition.....	860	1.3	42	43	98	2
63	4	Malnutrition.....	740	1.8	40	40	100	0
64	2	Malnutrition.....	550	1.6	68	68	100	0
65	2	Malnutrition.....	610	1.7	31	35	89	11
71	6	Malnutrition.....	755	1.5	40	42	95	5
60	3	Normal.....	600	1.3	30	50	70	30
66	10	Rachitic.....	620	2.9	50	60	77	23
Aver.	5.3	.....	695	1.74	43	48	89	11

Folin and Denis,[14] in reporting results by their method, mention seven infants whose phenol excretion averages 48 mg., as shown in Table 3.

14. Folin, O., and Denis, W.: The Excretion of Free and Conjugated Phenols and Phenol Derivatives, Jour. Biol. Chem., 1915, **22,** 309.

The weight of these infants is not mentioned, nor is the number or character of their stools. The amount and character of diet is also omitted. However, the comparatively large excretion of urine, total nitrogen, and phenol would indicate, as compared with our cases, that these infants were given artificial food.

A rather striking fact is found in Cases 63 and 64, in that the free phenol equals the total phenol. Whether these results were verified by other tests on these specimens is not stated. In the cases included in this investigation it was found several times that the amount of free phenol equaled or exceeded the total phenol. However, carefully repeated experiments on these same specimens showed that the error was due to the loss of phenol by evaporation during heating.

Nevertheless, Folin and Denis' general average of 89 per cent. of free phenol and ours of 83 per cent. show what a remarkably large percentage of the phenol is excreted in the free form; this, too, in spite of the fact that the latest text books on biochemistry (Hammarsten, Matthews, Hawk, and Neubauer and Huppert), so far as they refer to this point at all, state the opposite.

To show that the number of stools per day has an effect on the excretion of phenol, as Folin believed and as Salkowski,[15] Brieger,[16] Russo,[17] and Strasser[18] have shown, we have gone over the clinical charts available on our cases and tabulated the findings in Table 4.

If one considers three stools per day to be normal for infants, then of the twenty-two comparisons here shown, ten are normal and twelve are abnormal. The average excretion of phenol by those having three stools per day or less is 26.1 mg., and for those having over three stools per day the average is 21.7 mg. If, however, one compares those having four or more stools with those having three or fewer, the results are more striking. The average phenol excretion of those having three stools or less per day is 26.1 mg. but for those having four stools or more per day the average is 16.2 mg.

A comparison of Cases 10 and 20, two children of the same age, whose total nitrogen excretions were 1.5 and 1.2 gm., respectively, and whose phenol excretions were 24 and 34 mg., apparently furnishes a striking example of the effect of diarrhea on phenol excretion. Whether this is due entirely to the enteral or to parenteral metabolism can hardly be considered a settled question.

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15. Salkowski, E.: Verschliessung des Darmkanals auf die Bildung der Karbolsäure im Körper, Berl. deutsch. Gesellsch., 1876, **9,** 1595; ibid., 1877, **10,** 842.

16. Brieger, L.: Ueber Phenolausscheidung bei Krankheiten and nach Tyrosinbebrauch, Ztschr. f. physiol. Chem., 1878, **2,** 241; Zur Kenntniss der Fäulnissalkaloids, Ztschr. f. physiol. Chem., 1882-1883, **7,** 274.

17. Russo, A.: Sulla eliminazione del fenolo delle urine, Revista clin. e. terap., 1888, Okt.; Abstr. Centralbl. f. klin. Med., 1889, **10,** 306.

18. Strasser, A.: Ueber die Phenolausscheidung bei Krankheiten, Ztschr. f. klin. Med., 1894, **24,** 543.

TABLE 4.—PHENOL EXCRETION WITH REFERENCE TO NUMBER OF STOOLS PER DAY

Number	Change in Weight During Investigation, Gm.	First Week		Second Week		Third Week	
		Number of Stools	Total Phenol, Mg.	Number of Stools	Total Phenol, Mg.	Number of Stools	Total Phenol, Mg.
6	— 360	2	35.6	3.1	31.2	1.3	29.1
7	+ 295	5.1	12.8	4.2	12.8	4	12
8	+ 600	4	29.5	2	41.8	5.4	29.3
9	+ 200	3.3	39.1	6.3	27.1	3.6	24.9
10	0	7	24				
20	— 50	1	33.8				
11	+ 90	7	10.5				
12	+ 30	3	22.7	4	21.1		
13	+ 40	2	13.6				
14	+ 80	1.3	9				
18	+ 120	1.5	17				
21	+ 210	2	36.7				
28	— 70	2	21.6				

Changes in weight have no demonstrable effect.

For the purpose of a further metabolic study with reference especially to artificial and breast feeding, the more important factors are summarized in Table 5.

The artificially fed infants show a phenol excretion of 8 mg. per kilogram of body weight; breast fed, 5 mg. per kilogram. Mayer[19] does not give the weights of all his infants. Nevertheless, he observed that "the decomposition in those fed on cow's milk allowed the formation of more phenol than in those fed on breast milk."

In so limited a number of cases any proportion must be ascribed partly to accident. In our fifteen cases the artificially fed compared with the breast fed show a phenol excretion ratio of 2 to 1, in Meyer's cases 3 to 1. Unfortunately, Meyer does not give the total nitrogen excretion in his cases, so we cannot compare results with reference to the protein intake.

That age and consequent increase of protein in the diet, as evidenced by total nitrogen excretion, have a decided effect on phenol excretion is indicated in the following averages:

Age	Total N, Gm.	Total Phenol, Mg.
4 to 6 months (6 cases)	1.454	34.3
1 to 3 months (7 cases)	0.763	25.5

19. Mayer, P.: Ueber Indroxyl-, Phenol-, und Glycuronsäureausscheidung beim Phloridzindiabetes, Beitr. z. Chem. Physiol. u. Path., 1902, **2**, 217.

It is also noteworthy that, without reference to age, an increase in total nitrogen is accompanied by an increase in total phenol. From our study a working rule might be formulated: *Trebling the protein intake doubles the phenol excretion.*

TABLE 5.—A COMPARISON OF DIETS

Number	Age, Mo.	Weight, Kg.	Urine, C.c.	Total Phenol, Mg.	Total Nitrogen, Gm.
Artificial milk					
4	3	4.3	705	58	2.89
5	6	3.6	726	55.8	1.26
6	6	5.1	781	30.9	1.917
8	4	3.5	698	31.9	1.303
9	4	4.4	605	30.3	1.526
10	6	5.3	799	24.0	1.528
12	2	4.7	583	21.9	1.686
20	6	4.9	210	33.8	1.192
18	3	3.7	225	17	1.185
Average	4.1	4.4	591	33.7	1.609
Breast milk					
7	2	3.2	420	12.6	0.426
11	1.25	1.8	465	10.5	0.382
13	0.5	2.9	150	13.6	0.264
14	0.25	2.9	34	9	0.293
21	1.50	5.9	402	36.7	0.412
22	2	2.8	155	21.6	0.358
Average	1.25	3.3	271	17.3	0.356

The nitrogen-phenol ratio in adults is shown by summarizing the cases reported by Folin and Denis[14] as follows:

Diet	Total N, Gm.	Total Phenol, Gm.
High protein (14 cases).....	18.76	0.443
Low protein (16 cases).....	5.98	0.24

These thirty cases were from the usual run of city hospital patients, including typhoid, pernicious anemia, carcinoma, pleurisy, and three cases of pneumonia with temperatures of from 103 to 104.

They also compared high and low protein diets in the same individual on each of three cases, with the following average results:

Diet	Total N, Gm.	Total Phenol, Gm.
High protein	19.2	0.428
Low protein	6.7	0.215

TABLE 6.—PHENOL EXCRETION OF—

No.	Name	Clinical Condition	Age in Hours at Start of 72 Hr. Spec.	Weight		Stools
				At Birth	Gain or Loss in 72 Hours, Gm.	
23	Lepisto.....	Pemphigus.....	8	2,710	—250	2, meconium
24	Schonning.....	Normal.....	36	4,215	+ 60	2, meconium; 1, △
25	Lohn.....	Normal.....	27	3,365	— 5	2, meconium; 1, △
26	Ranta.....	Icterus, pemphigus.....	3	3,725	—585	3, meconium
27	Kester.....	Icterus.....	38	4,090	—250	1, meconium; 1, △
28	Bromberg.....	Perioral dermatitis.....	1	3,505	—310	2, meconium; 1, △
29	Tish.....	Icterus.....	12	2,945	— 40	2, meconium
30	Hatcher.....	Icterus.....	17	2,990	—225	2, meconium; 1, △
31	Strander.....	Normal.....	22	3,355	—260	2, meconium; 1, △
32	Jorgensen.....	Icterus.....	0.5	3,630	—440	2, meconium
33	Anderson.....	Icterus.....	1	4,115	—325	2, meconium
35	Anderson.....	Icterus.....	1	3,585	—440	3, meconium
36	Moore.....	Icterus.....	0	3,690	—290	1, meconium
37	Anderson.....	Normal.....	0.5	2,805	—265	2, meconium
38	Peterson.....	Normal.....	2	3,650	—310	3, meconium
39	Conklin.....	Normal.....	0	3,025	.....	2, meconium
40	Rohl.....	Pale, cephalhematoma...	0.5	4,630	—250 in 48 hours	○
41	Arkell.....	Icterus.....	1	3,275	—255	3, meconium
42	Olson.....	Normal.....	2	4,215	—475	1, meconium; 1, △
Average.....		.....	..	3,655	.....	.....

It is to be noted that this rule—trebling the protein doubles the phenol—which was worked out on infants, applies also to adults, when considered collectively.

In comparing the results of Folin and Denis in their experiments on infants (Table 3) with the fifteen included in this investigation (Table 1) and applying the rule given above, we find an explanation for their average of 48 mg. as compared with ours of 29 mg.

Total N	:	Total N	::	Phenol	:	Phenol
1.74	:	1.107	::	48	:	x (=30)

If it be true that the excretion of nitrogen and of phenol bears a definite relation both in infancy and adult life, without reference to disease, weight, length of bowel or number of stools, may it not be

—Newborn Infants in Nineteen Cases

Temperature Range in the 72 Hours	Urine							Remarks
	Volume, C.c.	Specific Gravity	Total Nitrogen, Mg.	Phenol				
				Free, Mg.	Total, Mg.	Per Cent. Free	Per Cent. Conjugated	
98 to 100.6	48	1.022	320	7.9	10.3	76	24	
98.6 to 99.4	93	1.026	1,427	16.7	20.2	82	18	
98 to 99.2	60	1.018	400	12.8	20.6	62	38	
98.6 to 103.6	47	1.027	382	15.6	19.9	77	23	May be a 48 hr. spec. only
98.6 to 100	69	1.024	853	15.4	23.4	66	34	
98.6 to 100.4	54	1.022	481	14.1	15.1	93	7	
97.8 to 98.4	36	1.018	147	7.8	8.3	85	15	
97.4 to 99	31	1.026	157	4.3	5.1	84	16	Received 15 c.c. water 5 hrs. before spec. started
98.2 to 99.2	55	1.024	610	12.1	13.4	90	10	Received 15 c.c. water 4 hrs. before spec. started
97.2 to 100.2	14	.....	94	1.2	2.9	41	59	
97.6 to 99	34	.....	275	11.8	14.6	81	19	
97.2 to 99.6	25	.....	127	7.4	8.5	87	13	
96.8 to 100	11	.....	39	1.8	2.1	86	14	
97 to 101	23	.....	198	4.6	5.7	80	20	
98 to 98.6	43	1.006	301	7.2	8.8	82	18	
96.4 to 98	33	1.011	199	4.6	6	77	23	
96.4 to 97.6	70	1.016	491	12.1	15.1	80	20	Died at 76 hrs. of subdural hemorrhage
96.2 to 100	7	.....	...	2.4	34	70	30	
96.6 to 100.8	34	1.016	280	8.6	9.9	86	14	
.....	41	.....	376	8.7	11.2	76	24	

true, as claimed by Blumenthal and Lewin,[20] that the phenol in the urine is also, in part at least, a product of endogenous metabolism?

Blumenthal and Lewin found an increased phenol excretion in cachetic cancer and increased protein catabolism following phloridzin injection. Mayer[19] and Schulz[21] were unable to verify these results in animal experiments after phloridzin injection.

The findings of Mayer and Scholz were accepted as correct by A. Ellinger.[22] He also accepted the statements of Senator[10] and of

20. Lewin: Phenol and Indoxyl im intermed. Stoffwechselen, Beitr. z. Chem., Physiol. u. Pathol. (Hofmeister), 1902, **50,** 472; cited from Meyer, L. F.: Footnote 11.

21. Scholz, H.: Beiträge zur Frage der Entstehung des Indicans im Tierkörper, Ztschr. f. physiol. Chem., 1903, **38,** 513.

22. Ellinger, A.: Neubauer and Ruppert's Analyse des Harns, **2,** 766.

Schild[23] as proof that phenol is formed only through bacterial action within the bowel, Schild having demonstrated that, in the hot summer months, the bowel is sterile for an average of twelve hours after birth.

Senator[10] tested the urine, liquor amnii, and meconium, using Baumann's[24] distillation method and testing the distillate with Millon's reagent. The conjugated sulphates (phenol and cresol) he converted into tribromphenol and tribromcresol. In testing the urine he used an average of 33 c.c., which must have required from one to three days to collect. Out of five tests on the urine only two were positive. The liquor amnii and meconium were both negative, as were also the stools until the children were a month or more of age.

The question of the origin of phenol seemed therefore to rest largely on their presence or absence in the urine of the new-born.

In an attempt to answer this question, using the Folin and Denis method modified as above described, urines were collected at the University of Minnesota hospital from the new-born during the first three days of life. The infants were treated according to the usual hospital routine, being put to the breast every four hours after the first half day. Only two cases (30 and 31) received any water during the three days and those only 15 c.c. each. The specimens were collected from male babies in the winter time and were preserved with chloroform and kept on ice. Nineteen cases in all were studied, with results as given in Table 6.

Phenol was present in every case, the amounts varying from 2.1 to 23.4 mg. The average urine volume for three days was 41 c.c., the average loss of weight 260 gm. If the weight at the end of the three days be used as a basis, the excretion per kilogram is 3.4 mg. This seems remarkable when we consider that this is practically a period of starvation.

The average total phenol excretion was 11.2 mg., of which 76 per cent. was free and 24 per cent. conjugated. The total nitrogen averaged 376 mg. Furthermore, compared with infants, the phenol content and total nitrogen are both low. If we apply the nitrogen-phenol rule to these cases we find, $1.74 : 0.376 : : 48 : x$ (10.4). The computed phenol result (10.4) approximates the obtained result (11.2) closely enough to indicate that when taken collectively, the nitrogen-phenol ratio in fasting new-born infants is approximately the same as in other infants and in adults.

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23. Schild, W.: Das Auftveten von Bacterien im Darminhalte Neuge borener vor der ersten Nährungsaufnahme, Ztschr. f. Hyg. u. Infectionskrankh., 1894, **19,** 113.

24. Baumann, E.: Ueber gepaarte Schwefelsaüren in Organismus, Arch. f. Physiol., 1876, **13,** 285.

SUMMARY

The Folin and Denis method of determining total phenol in the urine gives more uniform results in cold weather when modified as here suggested.

An increase in the number of stools per day is associated with a decrease in the total phenol output.

In this series of fifteen infants the phenol excretion per kilogram of body weight is less in the breast-fed than in the artificially fed infant.

In infants and in adults, so far as it is possible to determine from the limited number of cases now at hand, there is an interrelation between the total phenol excretion and the protein intake as measured by the total nitrogen excreted in the urine. This relation can be expressed in the general term, *trebling the protein intake doubles the phenol excretion.*

Contrary to the earlier findings, phenol is quantitatively present in the urine of every new-born infant, the average of these nineteen cases being 11.2 mg. for the first three days of life.

As phenol is present during this period of starvation, it must originate in part through endogenous metabolism.

I am gratefully indebted to Dr. Fritz B. Talbot of the Massachusetts General Hospital, Dr. Henry I. Bowditch of the Boston Floating Hospital and Dr. J. P. Sedgwick of the University of Minnesota Hospital, for the careful collection of the urine specimens and for the clinical data on these cases.

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STUDIES IN THE CHEMISTRY OF THE SPINAL FLUID OF CHILDREN *

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Due in part to the fact that a new method for the treatment of chorea, necessitating the frequent withdrawal of spinal fluid, has been used at the hospital[1] we were fortunate enough, during the past year, to obtain for examination the spinal fluids from a rather large number of children. It appeared of interest to examine these fluids for their nonprotein nitrogenous constituents and their reducing substances, by means of the newer methods of Folin and Denis and their co-workers.

NONPROTEIN NITROGENOUS CONSTITUENTS

Up to the present, no examinations appear to have been made of the spinal fluid for its nonprotein nitrogenous constituents (total nonprotein nitrogen, urea, uric acid, and creatinin) by means of the accurate and relatively simple methods of Folin and Denis and others.[2] Woods[3] examined the spinal fluid in chronic nephritis for total nonprotein nitrogen and urea. He found that the total nonprotein nitrogen was, as a rule, 25 per cent. lower than that of the blood. The urea content of the spinal fluid approximately equaled that of the blood. Cullen and Ellis[4] found the concentration of urea in the spinal fluid the same as that in the blood. While our work was in progress, Myers and Fine[5] reported the results of their analysis of the spinal fluids from fifteen cases of nephritis in adults. Their conclusions were that the concentration of urea in spinal fluid averaged 88 per cent. of that in the blood; the concentration of creatinin averaged 46 per cent. of that in the blood; the concentration of uric acid averaged 5 per cent. of that in the blood; and the concentration of sugar averaged 57 per cent. of that in the blood.

REDUCING SUBSTANCE

Very few contributions have been made to the chemistry of the reducing substance of the spinal fluid. According to Mott,[6] Claude

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* From the A. Jacobi Division for Children and the Pathological Laboratory of the German Hospital, New York.

1. Goodman, A. L.: Arch. Pediat., 1916, **31,** 649.
2. Leopold and Bernhard: Am. Jour. Dis. Child., 1916, **11,** 432.
3. Woods, A. C.: Arch. Int. Med., 1915, **16,** 577.
4. Cullen and Ellis: Jour. Biol. Chem., 1915, **20,** 511.
5. Myers and Fine: Proc. Soc. Exper. Biol. and Med., 1916, **13,** 126.
6. Mott, F. W.: Lancet, London, 1910, **2,** 1, 79.

Bernard demonstrated the existence of sugar in the spinal fluid. Halliburton came to the conclusion that the reducing substance was not sugar, but pyrocatechin. He later abandoned that view, however, and, according to Mott, now agrees with the great majority of other observers, that the reducing substance is glucose, and that it is always present in the spinal fluid in normal conditions. Schloss and Schroeder[7] recently examined normal and pathologic spinal fluids in children for their sugar content, employing the Lewis and Benedict method. They found that the sugar content in normal fluids varied between 0.05 and 0.139 per cent. They also demonstrated that the sugar content is usually reduced in all forms of meningitis, although it may at times be normal in tuberculous meningitis. In infantile paralysis, syphilis, and idiocy the sugar content was normal. Connell[8] considers the absence of sugar in the spinal fluid a certain sign of meningitis, but its presence is no absolute proof that meningitis does not exist. The sugar content of the spinal fluid was investigated by Kopetzky[9] in eight normal cases, by means of the Benedict method; he found that it varied between 0.02 and 0.04 per cent. According to the same observer, in "the estimation of the presence of the carbohydrate body in the spinal fluid, and the determination of its absence, we have one of the earliest and most reliable signs of meningitis, and later a reliable test to afford information as to the progression or retrogression of the infection of the meninges."

PERSONAL STUDIES

We have examined the spinal fluids of fifty-nine children for nonprotein nitrogen, urea, uric acid, creatinin and sugar. The reaction of the spinal fluid was tested with litmus paper in every case. A cell count, globulin test, and Wassermann reaction were also done.[10]

METHODS

The methods employed for the nonprotein nitrogenous constituents were those of Folin and Denis and their co-workers, as described by us in a previous communication.[2] A modification of the Lewis and Benedict method was used in our sugar estimation.[11]

The results of the examination of ten normal spinal fluids withdrawn for diagnostic purposes are shown in Table 1. The nonprotein nitrogen varied between 17 and 26 mg. per 100 c.c. of fluid, the average

7. Schloss and Schroeder: Am. Jour. Dis. Child., 1916, **11**, 1.
8. Connoll: Quart. Jour. Med., 1909, **3**, 152.
9. Kopetzky: Research Prize, Am. Laryngol., Rhinol. and Otol. Soc., Philadelphia, 1912.
10. Done by Drs. H. Cohen, Saunders, Gordon and Fuller of the house staff of the German Hospital.
11. Myers and Fine: Essentials of Path. Chem., 1915.

amount being 21 mg. The urea varied between 7 and 13.5 mg. per 100 c.c. of fluid, the average amount being 9.9 mg. The creatinin varied between 0.7 and 1.5 mg. per 100 c.c. of fluid, the average amount being 0.9 mg.

In the normal spinal fluids examined there was a slightly positive reaction present for uric acid in a few cases, but in not a single instance was there enough uric acid present to give a positive quantitative test. Myers and Fine[5] have shown that in cases of nephritis the concentration of uric acid averaged only 5 per cent. of that in the blood. According to Cushing[12] the cerebrospinal fluid is chiefly secreted by the choroid plexus. The cells of the choroid plexus are relatively impermeable to

TABLE 1. —ANALYSES OF THE SPINAL FLUID IN NORMAL CHILDREN

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
2278	F.	5	21	Alk.	36	8.5	0	0.7	0.07	6	0	0	0
2279	F.	1½	23	Alk.	19	7.5	0	0.7	0.07	3	0	0	0
2334	M.	10	51	Alk.	23	9.5	0	0.7	0.07	25	0	0	0
2461	F.	8	44	Neut.	17	8.5	0	1	0.07	3	0	0	0
2648	F.	9	50	Alk.	19	10.5	0	1.5	0.07	1	0	0	
2615	F.	9	53	Alk.	23	11.5	0	1.5	0.07	2	0	0	
3134	F.	2	19	Neut.	20	7	0	0.7	0.1	41	±	0	
3204	M.	1½	18	Alk.	20	10	0	1	0.08	6	0	0	
3940	M.	5	..	Alk.	22	12.5	0	1	0.09	..	..	0	
3978	M.	4	32	Alk.	24	13.5	0	1	0.07	3	0	0	0
Average					21	9.9	0	0.9	0.07				

the passage from the blood stream of drugs and such substances as bile pigments, which in conditions of jaundice quickly stain all body tissues and fluids. From the results of our analysis we must conclude that uric acid, one of the constituents of the blood, does not pass readily through the choroid plexus into the spinal fluid in normal individuals.

The sugar content of the spinal fluid was very constant, and varied between 0.07 and 0.1 per cent., the average content being 0.07 per cent. These figures correspond very closely with those given by Schloss and Schroeder,[7] and are considerably higher than those reported by Kopetzky.[9]

In Table 2 are shown the figures obtained in the analysis of the spinal fluid as compared with the blood of normal children. Our

12. Cushing: Jour. Med. Research, 1914, **31,** 1.

results show that in normal cases lower values for the nonprotein nitrogenous constituents are obtained in the spinal fluid than in the blood. The average concentration of the nonprotein nitrogen in the spinal fluid averaged 75 per cent. of that in the blood; the average concentration of urea in the spinal fluid averaged 82 per cent. of that in the blood; and the average concentration of creatinin in the spinal fluid averaged 60 per cent. of that in the blood.

TABLE 2.—COMPARISON BETWEEN NONPROTEIN NITROGENOUS CONSTITUENTS AND SUGAR OF BLOOD AND SPINAL FLUID

	Nonprotein N, Mg. per 100 C.c.	Urea N, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Sugar as Dextrose, Mg. per 100 C.c.
Blood	28	12	1.8	1.5	0.1
Spinal fluid	21	9.9	0	0.9	0.07

FLUIDS FROM DISEASED CHILDREN

The results of the analysis of the spinal fluid in twenty-one cases of chorea are given in Table 3. It is of interest to note that the figures obtained for the nonprotein nitrogenous constituents and for the reducing substances showed no variation from the normal. The cell count was above normal in only four cases. The globulin reaction was negative in every case but one, in which the result was doubtful. The Wassermann reaction of the spinal fluid was invariably negative. From the negative Wassermann reactions obtained in our cases we conclude with Morse and Floyd[13] that syphilis plays no direct part in the etiology of chorea. In one case of chorea with severe symptoms of long duration the *Streptococcus viridans* was found in the spinal fluid.

Tables 4, 5, and 6 give the results of the examination of the spinal fluid in cases of idiocy, syphilis, epilepsy, and enuresis. The findings showed no changes from the figures obtained in normal cases.

The spinal fluid was examined in two cases of acute nephritis (Table 7). One case without uremic symptoms showed a slight increase in the total nonprotein nitrogen. There was present a trace of uric acid, which was not observed in normal cases. The urea, creatinin and sugar content were normal. In one case of nephritis with uremic symptoms the total nonprotein nitrogen, urea and creatinin were markedly increased. There was present a trace of uric acid. A comparison of the figures obtained in the spinal fluid and in the blood is shown. The latter were very much higher than those obtained in the spinal fluid.

13. Morse and Floyd: AM. JOUR. DIS. CHILD., 1916, **12**, 61.

We have examined the spinal fluid (Table 8) in one case of serous meningitis secondary to pneumonia, three cases of tuberculous meningitis, two cases of cerebrospinal meningitis, and one case of streptococcus viridans meningitis. In the case of serous meningitis the nonprotein nitrogenous constituents and the sugar content were within normal limits, the globulin reaction was negative, and the cell count was normal. In three cases of tuberculous meningitis the total nonprotein

TABLE 3.—ANALYSES OF SPINAL FLUID IN CHOREA

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
1777	F.	8	49	Neut.	24	8.5	0	1.3	0.08	6	0	0	
1889	F.	12	55	Neut.	..	12	0	1	0.08	4	0	0	
2358	M.	8	39	Alk.	22	9	0	1	0.07	3	0	0	
2539	M.	7	41	Alk.	25	11	0	1.5	0.08	—	—	0	
2494	F.	4	35	Alk.	24	11.5	0	1.1	0.08	4	0	0	
2525	F.	5	38	Alk.	21	10	0	0.7	0.07	1	0	0	
1889	F.	12	54	Alk.	25	12.5	0	1	0.06	4	0	0	
2791	M.	6½	45	Alk.	25	10.5	0	1	0.08	3	0	0	0
2746	F.	7	50	Alk.	22	9	0	1	0.07	4	0	0	
3060	F.	8	42	Alk.	24	13	0	1	0.07	7	0	0	
2947*	M.	11	67	Alk.	20	10.5	0	1	0.06	11	0	0	0
3558	F.	13	94	Alk.	21	9.5	0	1	0.07	5	0	0	0
3060	F.	8	42	Alk.	18	9	0	1	0.07	4	0	0	0
3751	M.	7	36	Alk.	24	10.5	0	1	0.08	0	0	0	
3742	M.	8	50	Alk.	25	12	0	1	0.08	31	±	0	
3932	M.	7	50	Alk.	24	14.5	0	1	0.07	4	0	0	±
4153	F.	9	47	Alk.	19	11.5	0	1	0.06	5	0	0	0
4354	M.	6	42	Alk.	25	13.5	0	1	0.07	12	0	0	
4819	F.	10	53	Alk.	24	12.5	0	1	0.05	5	0	0	
4794	M.	11	69	Alk.	30	16	0	1	0.06	3	0	0	
3960	F.	8	52	Alk.	24	11.5	0	1	0.07	28	0	0	

nitrogen and the urea were normal. The creatinin was slightly increased in two cases, and was normal in one case.

Uric acid was present in every case of tuberculous meningitis. In one instance there was a trace of uric acid, and in the other two cases 0.7 and 1.2 mg., respectively, per 100 c.c. of fluid. The sugar content was normal in one case and reduced in two. The globulin reaction was invariably positive. The cell counts were much increased. In two cases of cerebrospinal meningitis, in which the meningococcus was

TABLE 4.—Analyses of Spinal Fluid in Idiocy

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
1358	F.	2	25	Neut.	21	9	0	1.5	0.06	14	+	0	0	Idiocy
662	M.	1	19	Alk.	21	10.5	0	2.4	0.08	4	+	0	0	Idiocy
1775	M.	6	33	Alk.	..	11	0	1	0.08	6	+	0	0	Idiocy
2445	F.	5	28	Alk.	21	11.5	0	1	0.06	5	0	0	—	Idiocy, mongolian
2565	F.	2	22	Neut.	23	11.5	0	1	0.06	3	0	0	0	Idiocy
2680	M.	6	51	Alk.	25	10.5	0	1.5	0.07	1	0	0	0	Idiocy, mongolian
3244	M.	8	46	Alk.	21	9	0	1	0.06	4	0	0	0	Idiocy

TABLE 5.—Analyses of Spinal Fluid in Syphilis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
7961	M.	10	55	Neut.	15	5	0	1.5	0.06	4	0	0	4+	Syphilitic synovitis
815	F.	14	61	Neut.	24	13	Faint trace	0.5	0.07	4	0	0	4+	Bone syphilis
3933	F.	7	44	Alk.	21	10.5	0	1	0.07	22	0	10+	4+	Syphilis
4024	M.	11	61	Alk.	19	9.5	0	1	0.07	4	0	0	4+	Syphilis

TABLE 6.—Analyses of Spinal Fluid in Miscellaneous Cases

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
2144	F.	8	62	Alk.	24	10.5	0	0.5	0.08	4	0	0	—	Enuresis
1136	M.	6	46	Neut.	25	9.5	0	1.5	0.07	40	+	—	—	Epilepsy
1611	M.	11	73	Neut.	21	12.5	0	1	0.08	5	0	0	—	Epilepsy

TABLE 7.—Analyses of Spinal Fluid in Acute Nephritis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Remarks
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
2208	F.	7	38	Alk.	33	13	Trace	0.8	0.08	8	0	0	—	Albumin in urine with many hyaline and granular casts; few coarse granular casts and red blood cells; phenolsulphonephthalein output 35 per cent. McClean ratio 57; blood pressure 120 mm.; severe edema; condition improved
2674	M.	3	26	Alk.	93	46	Trace	2.4	0.12	60	0	0	—	Albumin in urine 0.15 per cent; many red blood cells and coarse granular casts; phenolsulphonephthalein output 4 per cent.; blood pressure 88 mm. mercury; uremia; condition improved
2674	Blood				170	116	2.5	5	0.15					

TABLE 8.—Analyses of Spinal Fluid in Meningitis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, Per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction		Diagnosis and Remarks
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood	
1845	M.	8	44	Neut.	11	6.5	0	1.0	0.1	8	0	0	...	Serous meningitis; lobar pneumonia; recovered
1778	F.	1½	18	Neut.	15	6.5	0.7	0.5	0.05	50	2+	0	...	Tuberculous meningitis; died
2851	F.	2	..	Neut.	10	4	Trace	2.2	0.08	900	4+	...	...	Tuberculous meningitis; died
2778	F.	5	39	Alk.	30	15	1.2	2.2	0.04	200	4+	...	...	Tuberculous meningitis; died
3303	F.	11	59	Neut.	21	9.5	0	1.9	0.04	100,000	4+	...	...	Cerebrospinal meningitis (diplococcus); improved
4081	F.	9	54	Alk.	21	9.5	0	1	0.06	4,400	4+	...	...	Cerebrospinal meningitis (diplococcus); recovered
2525	F.	6	39	Alk.	15	7.5	0	1.1	0	420	4+	...	...	Streptococcus viridans; died

TABLE 9.—Analysis of Spinal Fluid in Infantile Paralysis

Case No.	Sex	Age, Yrs.	Weight, Lbs.	Reaction	Nonprotein Nitrogen Constituents, Mg. per 100 C.c.				Sugar as Dextrose, per Cent.	Cell Count	Globulin Reaction	Wassermann Reaction	
					Nonprotein N	Urea N	Uric Acid	Creatinin				Spinal Fluid	Blood
4404	F.	1½	19	Alk.	25	12	0	1.7	0.07	24	2+	0	
4523	F.	3	30	Alk.	33	14.5	Faint trace	1.8	0.08	564	0	0	
4808	F	2½	26	Alk.	21	10.5	0	1.5	0.06	6	1+	0	
5049	F.	3	..	Alk.	26	10.5	0	0.5	0.05	14	0	0	
5106	M.	2½	..	Alk.	..	13	0	0.5	0.09	50	0	0	

found, the nonprotein nitrogenous constituents were normal, there was no uric acid present, the sugar content was reduced in both cases, the globulin reaction was positive, and the cell counts were enormously increased. Both patients recovered. In one case of meningitis in which the *Streptococcus viridans* was found, the nonprotein constituents were normal, but sugar was entirely absent from the spinal fluid. The cell count was markedly increased, and the globulin reaction was positive. The patient died.

Five cases of infantile paralysis were examined (Table 9), all in the early stages of the disease. The nonprotein nitrogenous constituents were within normal limits, but a trace of uric acid was found in one case. The sugar content was normal. The cell count was increased in all but one instance and the globulin reaction was positive in two patients, and negative in three.

SUMMARY

Chemical examination of the spinal fluid in ten normal cases in children gave the following results: The total nonprotein nitrogen varied between 17 and 26 mg. per 100 c.c. of fluid, the average being 21 mg.; the urea nitrogen varied between 7 and 13.5 mg., the average being 9.9 mg.; the creatinin varied between 0.7 and 1.5 mg., the average being 0.9 mg. In no case was there enough uric acid present in the spinal fluid to give a positive quantitative test. The sugar content varied within very narrow limits (0.07 and 0.1 per cent), the average being 0.07 per cent. The figures for the nonprotein nitrogenous constituents and the sugar content were lower in the spinal fluid than in the blood, in normal children. The concentration of total nonprotein nitrogen in the spinal fluid averaged 75 per cent. of that in the blood, the urea 82 per cent. of that in the blood and the creatinin 60 per cent. of that in the blood.

The chemical examination of the spinal fluids from diseased children showed the following conditions:

1. In chorea the chemical examination of the spinal fluid for its nonprotein nitrogenous constituents gave results closely paralleling those obtained in normal children.

2. Chemical examination in cases of idiocy, syphilis, epilepsy, and enuresis gave similar results.

3. In acute nephritis without uremic symptoms the total nonprotein nitrogen was slightly increased and uric acid was present in small amounts. In acute nephritis with uremic symptoms the total nonprotein nitrogen, urea and creatinin were markedly increased and uric acid was present in slight amounts. The sugar content was also increased. The figures obtained in the analysis of the spinal fluid were lower than those from the blood.

4. In serous meningitis the nonprotein nitrogenous constituents, as well as the sugar content were within normal limits. In tuberculous meningitis the total nonprotein nitrogen and the urea were normal, but the creatinin was slightly increased. Uric acid was present in every case, but the sugar content was normal or slightly reduced. In cerebrospinal meningitis the nonprotein nitrogenous constituents were normal, but the sugar content was reduced. In a fatal case of meningitis in which the streptococcus was found, the nonprotein nitrogenous constituents were normal and sugar was absent.

5. In the early stages of infantile paralysis the nonprotein nitrogenous constituents, as well as the sugar content, were within normal limits.

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ALKALI AND EARTH ALKALI EQUILIBRIUM IN SPASMOPHILIA *

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In 1913 I published an article[1] on some work done in regard to the relationship of salts in spasmophilia which was the result of experiments on dogs and of clinical observation. In that work I came to the following conclusions:

1. In dogs in which a hyperirritability of the nervous system existed, as shown by the increased electrical irritability, and as produced by removal of the thyroid gland, there is no regular variation in the formula $\frac{Ca}{Na}$ or $\frac{Ca + Mg}{Na + K}$ before and after operation, as shown by metabolic experiment. While in three dogs thus examined there was apparently some support of the proposition that the quotient of this formula is increased during the period of hyperirritability of the nervous system, in the fourth dog no such action could be noticed.

2. In estimating the salt content of the brain of five dogs, the first being a control, there was regularly found a decrease in the calcium content in the thyroidectomized animals. In one instance, however the formula $\frac{Ca}{Na}$ was less than that of the control animal.

3. No variation in electrical irritability or severity of the convulsive period could be demonstrated by intraperitoneal injections of normal sodium and calcium salts in the quantity of from 40 to 45 c.c. of sodium salts, and from 2 to 4 c.c. of calcium salts in twenty-four hours.

4. Even under normal conditions, when carefully estimated, the electrical irritability in dogs varies quite widely.

5. While food containing whey is distinctly irritating to spasmophilic infants, the sodium and potassium salts corresponding in quantity to those contained in the whey do not regularly produce the increased electrical irritability which one would expect were the sodium to be regarded as the irritating substance in the whey.

6. This failure of the sodium and potassium to produce results may be explained either by the fact that the forms in which the sodium and potassium were given, that is, sodium chlorid and calcium chlorid, were not readily absorbed in the gastro-intestinal canal, or that these salts were not in themselves the irritating factors. The latter proposition would seem to be much more probable.

It will be seen, therefore, that these experiments have brought little or no confirmation of the hypothesis that the increased electrical irritability in spasmophilia is the result of a disturbance of calcium and sodium equilibrium.

Since that time numerous articles have appeared on this subject, mostly with the idea of determining whether calcium salts had the effect in spasmophilic infants of reducing irritability.

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* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

1. Grulee: Am. Jour. Dis. Child., 1913, **5**, 205.

Freudenberg and Klocman[2] report the reduction of electrical irritability by the use of calcium saccharate, though this was not especially successful, but lipocalcin, a fat-calcium synthetic product, seemed to have a definite effect.

Grünfelder[3] obtained a more rapid and lasting result with calcium-bromid than with sodium bromid in these cases.

Blühdorn[4] lays stress on the fact that only with the use of large quantities of the calcium salts can any effect be produced. With high dosage the action of the calcium occurs within a few hours. He advises the use of from 2 to 3 gm. of calcium chlorid or bromid daily.

In this connection the findings of Behrend[5] are very interesting. Behrend found that magnesium sulphate was of the greatest value. He used an 8 per cent. solution of anhydrous magnesium sulphate. From 15 to 20 c.c. of this solution were given subcutaneously and repeated as often as necessary, intervals being never less than twenty-four hours. The results which he obtained were very satisfactory.

McCallum and Vogel[6] found that the blood of animals in tetany was very poor in calcium and that administration of parathyroid extract did not increase this calcium content. On the other hand, if the extirpation had been incomplete, tetany did not appear and the calcium content of the blood was that of the normal animal. They say:

> In spite of our efforts to shake the theory that tetany is closely dependent on the disturbance of the calcium content of the blood, it is supported by stronger evidence than any other idea, but much remains to be done before a clear conception of the process is reached.

In a recent editorial[7] in the *Journal of the American Medical Association* there appeared the statement:

> The treatment for spasmophilic convulsions is purgation unless the child has already had a severe diarrhea. Breast milk should be given if possible, if the patient is an infant, otherwise the food should be starchy, as barley water or oatmeal gruel. *Some alkali, as potassium citrate, is advisable.* Lime water should be given in teaspoonful doses five times a day.

It is very evident that the writer of this editorial does not believe in the disturbance of the alkali earth-alkali equilibrium in these cases, and it is also quite likely that the advice here given is given because of the hypothesis that spasmophilia may be in some way associated with acidosis. This would seem perhaps to be supported by the findings of Liefmann,[8] who demonstrated an increase of the acetone output of the urine.

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2. Freudenberg and Klocman: Jahrb. f. Kinderh., 1913, **78,** 47.
3. Grünfelder: Therap. Monatsch., 1913, **27,** 416.
4. Brühdorn: Monatsch. f. Kinderh., 1914 (Orig.), **12,** 185.
5. Behrend: Monatsch. f. Kinderh., 1914 (Orig.), **12,** 269.
6. McCallum and Vogel: Jour. Exper. Med., 1913, **18,** 618.
7. Editorial: Jour. Am. Med. Assn., 1916, **66,** 274.
8. Leifmann: Jahrb. f. Kinderh., 1913, **77,** 125.

In regard to the question of the effects of alkali on spasmophilia, two very interesting articles have appeared. Lust[9] reports a case of tetany in a 2-year-old girl, in which he felt that he could recognize a very definite connection between sodium chlorid administered in quantities of 3 to 5 gm. per day and water retention, with, at the same time, a definite increase of electrical irritability. He also saw an increase as a result of administering potassium chlorid in quantities of 0.5 gm. per kilogram per day; the successes noted were on the anodal reaction, not the cathodal.

Brown and Fletcher[10] believe that tetany is due to the retention of water, in which way the sodium salts are held in the body with a resulting increased irritability due to these salts. By diuresis they think one can obtain the best results in these cases, explaining this on the basis of the excretion of the sodium salts from the system.

The work of Zybell[11] is the most extensive on this subject, and I will take up only that part of his work which relates to the effect of the various salts. He noted the action of calcium thirty-four times in twenty-two children, the ages ranging from 2⅘ to 22½ months; five children were in the second year, and eight were less than 6 months old. His patients were frequently troubled with vomiting after the use of a 2.5 per cent. solution of calcium chlorid given in teaspoonful doses at various intervals. In four cases only once was there a decrease of the opening contraction of more than 1 ma. There was no marked difference to be noted with doses as great as 3 gm.; there was no bettering of the laryngospastic or eclamptic seizures; the quantity of calcium seemed to make no difference.

As to the magnesium salts, five cases were tested; a 3 to 5 per cent. solution of magnesium borocitrate was used; no toxic effects were noticed. The reaction in this case was slow. After four hours there was a gradual decrease in the electrical irritability; in no case, however, did the irritability return to normal or change the clinical picture. In testing the sodium salts sodium chlorid and sodium sulphate were used. In five cases examined sodium chlorid 3 to 6 gm. was given; in six and one-fourth hours there was noted an increase of 1 ma. in anodal and cathodal reactions. In two cases, however, the increase was no different from that which had been found in the case in which the food had been withdrawn. With potassium his experiments were carried on with potassium acetate in doses of 30 to 50 c.c. of a 10 per cent. solution. In each case there was a transitory increase of the cathodal opening contraction of from 0.5 to 0.9 ma. After removal of the potassium, irritability immediately went back to its former figure, so that the connec-

9. Lust: München. med. Wchnschr., 1913, **60,** 1482.
10. Brown and Fletcher: Am. Jour. Dis. Child., 1915, **10,** 313.
11. Zybell: Jahrb. f. Kinderh., 1913, **78,** Supplement No. 29.

tion between the increase of the irritability and potassium can scarcely be denied. In a general way it can be said that Zybell's experiments are iconoclastic, since they place in doubt nearly everything which has previously been done on the effects of salts on spasmophilia, and it would seem that this work would need very careful confirmation in order to make it of value.

The observations which I present have been carried out within the past year at the Presbyterian Hospital, Chicago, and consist in a report of six cases in which the effect of the oral administration of large amounts of calcium salts and of sodium and potassium salts were observed. The effects on the cathodal opening contraction will be the only ones noted in this paper. In the early stages in every case it will be seen from the charts that calcium reduced the electrical irritability, while with the sodium and potassium salts there was seen to be an increase in the irritability. The effects of these salts were much less marked as the irritability approached the normal.

Such a case as that of Lillie S. is especially interesting, as the electrical irritability had been at from 2.5 to 3.5 ma. for a full week, when on administrating sodium and potassium for forty-eight hours the electrical irritability rose to 1 ma., then with the administering of calcium the electrical irritability dropped to 4 ma. and the further giving of sodium and potassium had no effect whatever on the curve.

The first of these cases was one which has a very interesting history, as will be noted in the record, and was the one which gave the clue to the observations made later. In this instance the child, who had been on the calcium treatment for tetany, was brought to the hospital suffering with a rather severe pyelocystitis; for this condition large quantities of alkali in the form of sodium bicarbonate and potassium citrate were given, with the result that the temperature was reduced and the pyelocystitis was apparently very much benefited. With the reduction of the temperature we were very much surprised to see the reappearance of the tetany. This again disappeared on the use of calcium salts; the electrical irritability was again raised with a renewal of the alkali.

It is very interesting to note with a careful observation of the weight curves (weight taken at the same time each day) the relationship between the retention of water and the increase of electrical irritability. While this seemed to take place in some instances, in others an increase of electrical irritability was frequently accompanied by a drop in weight. These observations were carried on under like conditions. The electrical irritability was taken at the same time each morning, between the hours of 9 and 10, with the same apparatus, under the same conditions, by the same individual, so that comparative readings were obtained. There was no change of food in the majority of the cases,

and in none of the cases was there to be noted a gastro-intestinal disturbance.

For the purpose of control, three nonspasmophilic persons were given like doses of sodium and potassium salts with no demonstrable effects upon the electrical irritability. It has been thought for some time by most observers that large quantities of calcium salts decreased electrical irritability and that removal of these salts would be followed by a return to an increased electrical irritability. It is quite likely that this return depends somewhat on the length of time of the administration of the calcium salts and the severity of the spasmophilic condition. It does not seem likely, however, that the simple removal of the calcium salts would always be followed by the definite reaction which is shown in these six cases in the early stages after the administration of sodium and potassium salts. Certain cases, such as that of Lillie S., speak distinctly against such an interpretation. While I do not feel that one would be justified in stating that the observations recorded give definite proof that there is a direct relationship between sodium and potassium salts and increased electrical irritability, or that spasmophilia rests on the question of equilibrium between the calcium and magnesium salts on the one hand and the sodium and potassium salts on the other, still it seems to me that the results here recorded do speak very strongly for some definite relation between increased electrical irritability and retention of sodium and potassium salts.

I recognize that much work must be done in order to establish such a fact. This cannot be done without exhaustive metabolism experiments or without examination of brain tissue under somewhat ideal conditions. It would seem to me, however, that if there is such a definite relation between the sodium and potassium on the one hand and calcium and magnesium on the other, the action of the sodium and potassium salts is not due primarily to retention of water in the system; or, if such is the case, we have no direct evidence to support such a theory and that we would have to suppose that in the observations here noted there had been marked destruction of tissue accompanied by distinct retention of water in those instances in which the electrical irritability was increased and the weight reduced.

Case 1.—Fay K., aged 6½ months, entered the Presbyterian Hospital April 8, 1915, assigned to Dr. Grulee, complaining of fever, general debility, and loss of weight. Three weeks previous to entrance the mother had noticed that the child, who up to that time had been perfectly well, began to grunt and acted as if distressed. She had chills and sweats, the temperature went up to 103.5, and she apparently had a convulsion, though she had no more after that. The child was put in warm blankets, and the condition seemed to improve, though she would take only about half her feedings, and three days later did not eat anything. The mother thought that the pain was in the head at that time, though enemas seemed to give the child some relief.

It was about this time that I first saw her, when she was taken to a hospital in Kenosha, Wis. The diagnosis was that of severe infection of the nose and throat. There was considerable vomiting at this time. The temperature fluctuated between 98 and 104. Examination of the ears proved negative. The condition apparently cleared up. About a week after the onset the child again developed a fever and when seen again by me in consultation she had a very typical carpopedal spasm, quite marked. This cleared up on the use of the usual treatment, calcium lactate, etc., when the child a third time developed a high temperature, and this time was sent to the Presbyterian Hospital, where she entered April 8, 1915. Previous to entrance the food had consisted of mother's milk with the addition of Mellin's food; later, Mellin's food alone.

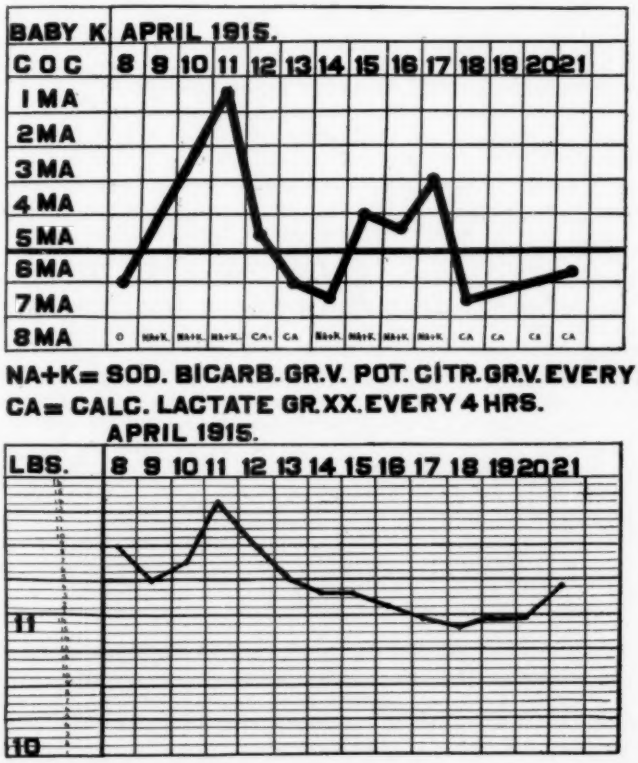

BABY K APRIL 1915.
C O C
8 9 10 11 12 13 14 15 16 17 18 19 20 21
1 MA
2 MA
3 MA
4 MA
5 MA
6 MA
7 MA
8 MA
NA+K= SOD. BICARB. GR.V. POT. CITR. GR.V. EVERY 2 HRS.
CA= CALC. LACTATE GR. XX. EVERY 4 HRS.
APRIL 1915.
LBS.
8 9 10 11 12 13 14 15 16 17 18 19 20 21
11
10

Fig. 1.—Record of Fay K. (Case 1), aged 6½ months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Of course the Mellin's food was put up according to the formula advised on the package, which included a fair quantity of milk. The stools could not be noticed because of the frequent enemas given for gas. Curds, however, were often seen, and constipation was never present. The urine was ammoniacal and stained the diaper. Three days before entrance the child did not urinate for sixteen hours. The bladder was distended and the baby seemed distressed. There was no apparent pain on urination. The urine seemed to cause some irritation in the genital region and about the buttocks. Other history, both of the child and mother, was negative.

Physical examination showed a rather apathetic child, undernourished. The head was well formed in its general outline. Posteriorly and below the occiput was a depressed area about the size of a dollar. On gentle pressure this could be slightly indented (craniotabes). The sutures were prominent. The anterior fontanel was about 2 inches in width. The ears and eyes were negative. There was a slight nasal discharge. The lips were dry and parched. The neck and chest were negative. The abdomen was at times flat and then distended with gas. The liver and spleen were not palpable. The extremities were negative. The reflexes were not increased. The surface of the body was extremely dry and hot and the skin somewhat scaly. The palms and soles were thickened, and the skin on the palms appeared calloused.

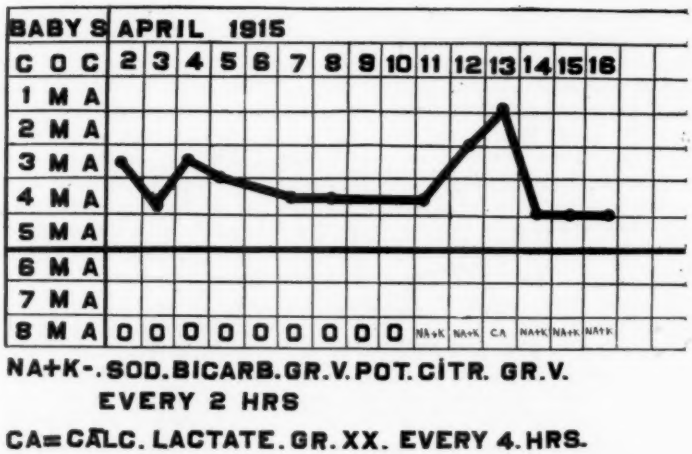
Clinical notes: On April 8 the electrical irritability was taken, and the cathodal opening contraction was 6 ma. The child on April 9 was put on potassium citrate and sodium bicarbonate, 5 grains each every two hours. On April 11 a typical tetany was present. The hands and feet were contracted with a tonic spasm. Edema was present, due to the contraction. Electrical irritability was greatly increased. The potassium citrate and sodium bicarbonate were stopped, and the child put on 20 grains of calcium lactate every four hours. By April 12 the tetany was found to be much less rigid, and the child was in much better condition. On April 13, on the same treatment, the child was in good condition, the edema was less and the tetany was much decreased. The child was then put on sodium and potassium again, with an increase of the electrical irritability on April 17 up to 3 ma. The child was then put back on calcium lactate, with a decreased electrical irritability. She left the hospital on May 10, the electrical irritability on May 6 having been normal. From April 17 on the child got 20 grains of calcium lactate every four hours. The child was on breast milk until April 17, when the food was changed to part breast milk and part albumin milk. On April 18 all the food became albumin milk, and this continued, with the exception of two days, until the child went home.

The temperature went above 100 only once during her stay in the hospital, when it was 100.2. From April 8 to April 14 the temperature ranged between 99 and 100. After that it was well within normal limits. On entrance the blood showed 22,000 white cells, and 65 per cent. hemoglobin. On April 19 the red cells were 5,150,000, white 11,600. The Wassermann was negative on two examinations. On entrance the urine showed about 10,000 leukocytes per cubic millimeter. This gradually cleared up under the use of hexamethylenamin. The catheterized specimen of urine showed staphylococcus in pure culture. The stool examination showed nothing of interest.

Case 2.—Lillie S., aged 7 months, entered the Presbyterian Hospital Feb. 17, 1915, on the service of Dr. Grulee. The complaint was that the child had had convulsions. These were first noticed three months previous to entrance, and had continued up to the time of entrance. There had been as many as ten a day, and at times the child had gone as long as a week without any. When the child was in one of these convulsions the eyes rolled and twitched, and the arms and neck muscles twitched. The seizure was usually not severe. The feeding had always been from the breast every three hours. The condition had always been good, the patient never having been sick. The bowel movements were normal.

On physical examination the patient was found to be very well nourished, well rounded, and fat. The head was round, and the anterior fontanel was about 1 inch in greatest diameter. The face was negative, the mouth and throat clear. There were no teeth. The abdomen and limbs were negative, the thighs extremely fat, the skin clear and normal, and there were no palpable lymph glands. The reflexes were normal. It is noted that on February 20 an enormous number of the *Bacillus coli* were found in the urine. The child during her first stay in the hospital showed a temperature ranging between 98 and 100.4. The apparatus for testing the electrical irritability at this time was out of order,

so that this was not taken. She was given chloral hydrate rectally 1 grain every four hours. The interval was gradually increased to six hours and then to eight. However, the dose was increased to 2 grains when necessary, and it was found necessary to give the child for the first three doses 2 grains. Calcium lactate, 20 grains every two hours, not to exceed six doses, was begun on February 20. It was then continued twice a day thereafter for three days. The child was breast fed throughout. Hexamethylenamin to the amount of 1 grain was begun on the 22d. At this time the blood showed 5,200,000 red cells, 8,100


BABY S APRIL 1915
C O C 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
1 M A
2 M A
3 M A
4 M A
5 M A
6 M A
7 M A
8 M A 0 0 0 0 0 0 0 0 0 NA+K NA+K CA NA+K NA+K NA+K
NA+K-. SOD. BICARB. GR. V. POT. CITR. GR. V.
EVERY 2 HRS
CA=CALC. LACTATE. GR. XX. EVERY 4. HRS.

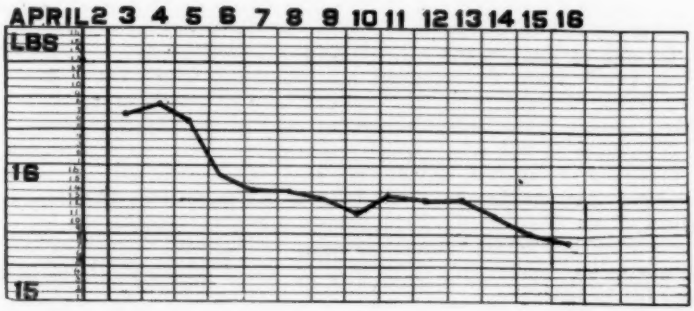


Fig. 2.—Record of Lillie S. (Case 2), aged 7 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

white and 85 per cent. hemoglobin. On February 18 the urine showed about 100 leukocytes per cubic millimeter, and a slight amount of nucleo-albumin. On the 20th the number of leukocytes was 250 per cubic millimeter, and the nucleo-albumin had increased in quantity. On March 2 there were to be found 500 cells per cubic millimeter. The child left the hospital on March 9 and returned again on the 18th with a renewal of the convulsions.

This history was that after leaving the hospital the child had had no convulsions until just previous to entrance, when they had begun to come at the rate of four a day. The child was still nursing from the breast, and there was

no other complaint. This child on entrance on March 18 was given 1 grain of chloral hydrate per rectum every four hours, and 20 grains of calcium lactate every three hours. The first electrical irritability test was made on March 2, when it was found that the cathodal opening contraction equaled 3 ma. Until March 11 the electrical irritability daily ranged not lower than 2.5 and not greater than 4 ma. For March 7, 8 and 9 the electrical irritability was 3.5 ma. On March 11 the child was put on 10 grains of sodium bicarbonate and 10 grains of potassium citrate every four hours, and the calcium lactate was stopped. On March 12 the cathodal opening contraction equaled 2 ma., and March 13 1 ma. The sodium and potassium were stopped and the child was again put on the calcium lactate, the amount previously given. On March 14 the cathodal opening contraction equaled 4 ma. The calcium was again stopped, and the sodium and potassium given a second time. From this time on the electrical irritability never went below 4 ma., the child remaining within normal limits until May 25. Until May 24 the child was given 5 grains each of sodium bicarbonate and potassium citrate every four hours. This was continued until May 29. On May 25 the cathodal opening contraction equaled 4.5 ma., on May 28 it equaled 4.5, and on May 29 5 ma. The amount of sodium bicarbonate and potassium citrate was then increased to 10 grains each, with the result that by June 5 the electrical irritability had fallen to cathodal opening contraction equal to 4 milliamperes. There had been a gradual and steady reduction.

The clinical notes show very little during this period. The temperature ranged between 98 and 100. On April 2 it rose to 103, but came down again within a few hours, and continued between the previous limits until the 17th, when the temperature again rose to 104. The highest on the following day was 103, then it dropped to normal and remained practically normal until May 7, when the child had a continuous temperature ranging between 101 and 102, until May 15. Then the temperature again came to normal and remained so until May 24, when it rose to 101.6, and on the 25th it went to 101.8, coming down to normal on the 26th, remaining normal on the 27th. But on that day it rose to 103.2, coming down again on the 30th and remaining so during the remainder of the child's stay in the hospital. There is no record of a convulsion after the child entered the hospital except that on April 3, at 9 a. m., just following the acute febrile stage, the child had one convulsion, which lasted four minutes, another lasting three minutes at 4:30 p. m., and at 7:45 p. m. another one lasting two minutes. The child during her stay at the hospital always showed some leukocytes in the urine, which probably accounts for the irregularity in temperature. For instance, on May 10 the number of leukocytes was found to be 5,000 per cubic millimeter. There was a leukocytosis of 16,200 on that day. On April 28 the blood count was 4,500,000 red cells, 15,500 white, of which 64 per cent. were small lymphocytes, 11 large lymphocytes, 4 transitional, and 46 polymorphnuclear neutrophils. On May 12 the child showed 9,000 leukocytes, on May 29 20,700.

There are no special clinical notes on this case except that on April 17 it was noted that though the child had been for seventy-two hours on sodium and potassium the urine was still acid.

Case 3.—Olga K., aged 5 months, entered the Presbyterian Hospital on the service of Dr. Grulee December 2, 1915, with a history of convulsions, cold in the head, and slow gain in weight. She had been born at home on July 7 previously, a midwife attending, the birth weight being 11 pounds, in a normal labor of two hours' length. The child had never been nursed, but had been bottle fed from birth. She had been fed according to the directions of the Infant Welfare Society. There were three to four stools a day, apparently of good consistency, and castor oil was used quite frequently. There were three other children in the family, aged 15, 13, and 11 years, respectively, all in school. The convulsions had begun the day before entrance, the child having had fifteen in the course of twenty-four hours. During an attack the infant grew rigid, the fists were clenched, the eyes rolled, and there was cyanosis. She coughed

after the convulsions for a few minutes, and then grew quiet. The child had had no convulsions for thirty-three hours previous to entrance. The gain in weight had been slow. She had had a cold in her head for five weeks, which had been growing worse, and there was some nasal discharge. Examination showed a fairly well-developed and fairly well-nourished child. Cradle cap was present, and the skin of the body was rather dry and easily irritated. All the glands, including epitrochlears, anterior and posterior cervicals, axillary and inguinal, were palpable. With this exception, nothing was noted of any value on physical examination. On December 4 her electrical irritability showed cathodal opening contraction approximately normal. On December 3 her blood count showed 5,260,000 red cells, 7,800 white, and 90 per cent. hemoglobin. The urine was negative, as was the throat culture. The Wassermann, both on the blood and the cerebrospinal fluid, was negative. For two weeks, beginning December 8, she was given 1/20 grain protiodid of mercury three times a day.

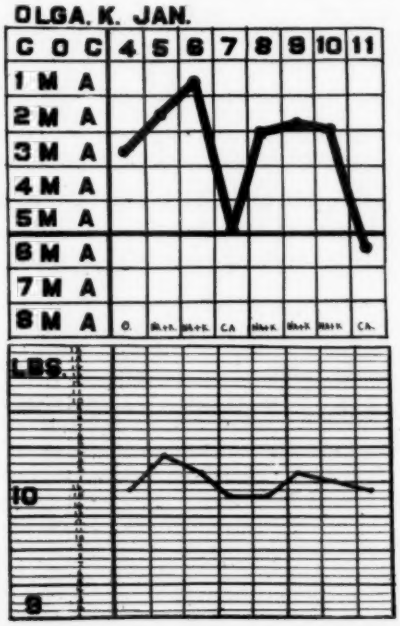


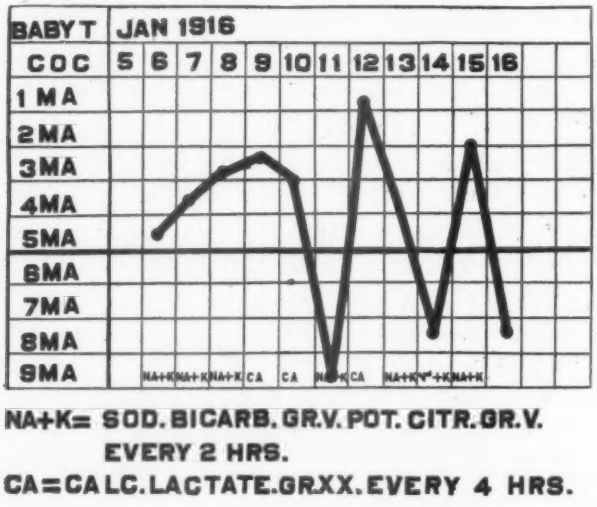
Fig. 3.—Record of Olga K. (Case 3), aged 5 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Her weight on entrance was 9 pounds, 9½ ounces. At the time of leaving on January 31, 1916, it was 10 pounds 3½ ounces. On January 4 her electrical irritability was taken, and it was found that she had a cathodal opening contraction equal to 2.5 ma. She was given 10 grains each of sodium bicarbonate and potassium citrate every two hours for the next two days, with the result that on January 5 the increase of electrical irritability was shown in a cathodal opening contraction equal to 1.5 ma., and on the 6th it equaled 0.5 ma. On January 6 the child was given 10 grains of calcium lactate every four hours, with the result that the cathodal opening contraction was raised to 5 ma.

Calcium was then discontinued, sodium and potassium being given again on January 8, 9 and 10. The reactions became 2, 1.75 and 2 ma. on the three respective days.

A slight laryngospasm was noticed on January 8, more marked on the next day, and less marked on the 10th. On this last day calcium was given again, with the result that on the 11th the cathodal opening contraction became 5.5 ma.

The child left the hospital on January 31 because of the development of a gonorrheal vaginitis.



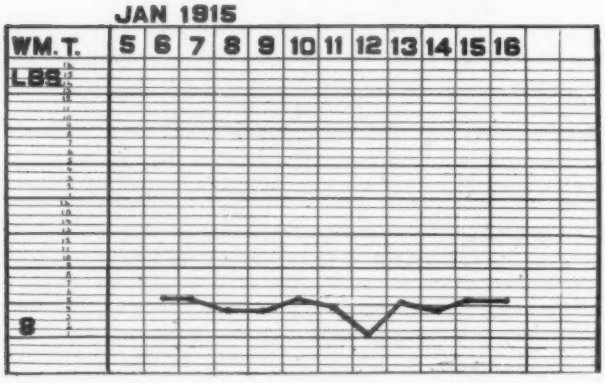


Fig. 4.—Record of William T. (Case 4), aged 3 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

Case 4.—William T., aged 3 months, entered the Presbyterian Hospital the first time on Dec. 9, 1915, on the service of Dr. Grulee, with the complaint of emaciation and constipation. The history obtained was imperfect, as it could be secured only through an interpreter. The child was born on September 2, 1915. It was the fifth child, weighed 9½ pounds (?), was born in two-hour normal labor, with midwife as attendant, and with vertex presentation. The child was bottle fed. The mother had nursed none but the first two children.

The child had been at an infant welfare station, where it had received its food. About a month previous to entrance, probably before having been taken to the infant welfare station, the child had had severe dysentery, from which it had not completely recovered. The emaciation had lasted from the time of the dysentery, as had also the constipation. Constipation had been treated with castor oil. There had been for a short time previous to entrance an alternating of constipation and diarrhea, the number of stools varying from one to ten or twelve a day. The stools were usually green, and varying from liquid to hard. The child showed a very irregular weight curve. The weight at entrance was 7 pounds 10½ ounces and when he left 8 pounds 8 ounces, his stay in the hospital having been about six weeks. During that time the food consisted, with the exception of the first day, of albumin milk, which was gradually increased from 18 to 24 ounces, and dextri-maltose increased from ½ to 1 ounce. From January 3 on there had been added ¼ ounce of flour ball to the day's feeding. The temperature showed a tendency to be rather subnormal, though occasionally points above the normal were seen. On December 10 the blood showed 5,880,000 red cells, 22,000 white and 80 per cent. hemoglobin. The urine was negative. A throat culture showed no diphtheria. On December 13 a few pus cells were found in the urine. This continued for a few days, after which the urine was negative. The number of pus cells in this case could hardly constitute a reason for calling the case one of pyelocystitis. On January 13 there is a clinical note that a furuncle on the outside of the right heel was incised and considerable pus removed. With this exception, the course of the child in the hospital was without incident, except for the electrical irritability. This increased electrical irritability was not accompanied by any signs of spasmophilia, although at times it was quite marked. On January 6 the cathodal opening contraction equaled 3.5 ma. Under sodium bicarbonate and potassium citrate, 10 grains of each every two hours, the cathodal opening contraction became 2.5, 1.7 and 1.25 ma. on January 7, 8 and 9, respectively. Calcium lactate, 20 grains every four hours, was now begun, with the result that on the 10th and 11th the cathodal opening contraction equaled 2 and 8.5 ma. on the two respective days. Again sodium bicarbonate and potassium citrate were given, and on January 12 the irritability was increased to 0.9 ma. As a result of the readministration of calcium lactate the irritability fell on January 13 to 3.5 ma. The sodium and potassium compounds were again administered as before, but the irritability on January 14, 15 and 16 was over 5, 2 and over 5 ma. on the three respective days.

Case 5.—Euphrosene G., aged 16 months, entered the Presbyterian Hospital on December 16, 1915, on the service of Dr. Grulee. She was the sixth child, born of a rapid normal labor, vertex presentation, weight 8½ pounds. She was fed three months on the breast, and then fed on modified milk for sixty-seven days previous to entrance. The mother said that the child had been drowsy and had slept too much. She also made strange noises while breathing. She had had a slight cough for the week previous to entrance, and some sneezing. There were some fever and chills. No treatment was given for three days previous to entrance. During her waking periods she seemed very much disturbed as she cried almost constantly. On physical examination the child was found to be well nourished and well developed. The fontanel was open. There were some few râles in the lungs posteriorly. The liver and spleen were not palpable, nor was there anything about the extremities except the lesions on the skin. These lesions were discretely distributed over the trunk posteriorly, left upper arm, and extended on surface of the legs. They were pigmented, at times crusted, small papules, from 2 to 4 mm. in diameter. There was some evidence of scratching. The posterior cervical, the axillary and the inguinal glands were palpable. Electrical irritability on the day of entrance 5 o'clock in the afternoon showed cathodal opening contraction equal to 4.5 ma. The child on entrance was given 10 grains of sodium bicarbonate, and 10 grains of

potassium citrate every two hours. On December 17 and 18 the irritability was increased to 2.5 and 0.75 ma., on the two respective days, and there was a definite laryngospasm. On December 18 the sodium and potassium were dropped and calcium lactate, 15 grains every four hours was given. On the 19th the electrical irritability was 6 ma. On December 19 the sodium bicarbonate and potassium citrate were again given. The electrical irritability became 4.5, 3.5 and 2 ma. on December 20, 21 and 22, respectively. On the 22d calcium lactate was again given. On the 23d the electrical irritability was cathodal opening contraction 7 ma. The calcium lactate was then stopped and the child given cod liver oil and phosphorus. On the 29th the electrical irritability showed 8 ma. During the time when the child was under observation for electrical irritability there was no change in the food. The weight during that time

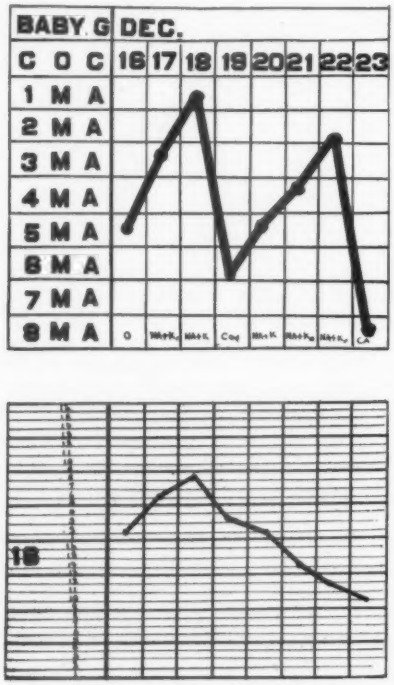


Fig. 5.—Record of Euphrosene G. (Case 5), aged 16 months. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

showed a steady decrease, except on the first two days (see weight curve). There was no increased fever, temperature remaining normal throughout the whole course. The blood count showed 5,430,000 red cells, 11,300 white and 75 per cent. hemoglobin. A throat culture proved negative for diphtheria. The urine was negative throughout.

Case 6.—George D., aged 8 months, entered the Presbyterian Hospital on Feb. 14, 1916, on the service of Dr. Grulee, with the complaint of convulsions, inability to cry, and loss of weight. The child was born on the previous June 9, weighing 6 pounds 12 ounces. He was the second child, born of an eight-hour normal labor, breech presentation. He was breast fed for six weeks

every two hours, then changed to artificial feeding because of insufficient breast milk. First he was put on milk and barley water every two hours, then on a formula of certified milk for two weeks. The stools became bad and the food was changed to a different formula and prepared food used, always given every two hours. Within the four days previous to entrance the child had been on a mixture of 20 ounces of whole milk, 10 ounces of water, ½ ounce of dextrimaltose, five feedings of 6 ounces each. The stools at the time of entrance were regular and normal. The convulsions began five weeks previous to entrance.

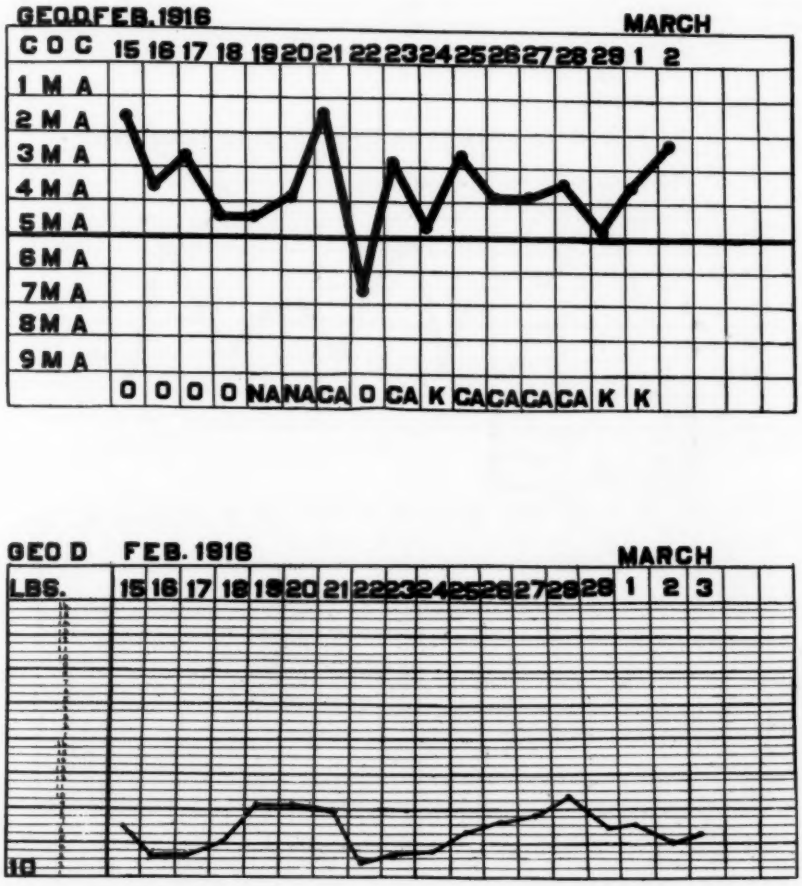


Fig. 6A.—Record of George D. (Case 6), aged 8 months. First period. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

There had been three on the first day, and three on successive days. There had been none after that time. The child, however, since the onset of the convulsions, had shown an inability to cry. It made the effort, but got very short of breath and could make no noise. Even before the convulsions occurred this tendency was present. There had been an indefinite loss of weight since the convulsions first occurred. For the previous few days the child, however, had

gained 10 ounces. On examination he proved to be an emaciated boy, who showed a very evident laryngospasm. The skin was negative except for a reduction of tissue turgor. The lymph glands were palpable in the anterior and posterior cervical, axillary, epitrochlear, intercostal, and inguinal regions. The head and the thorax were negative, and the abdomen negative except for right inguinal hernia. On February 18 it was noted that the von Pirquet was negative. On February 22 it was noted that the spinal dulness reached to the seventh dorsal spine. On March 4 the child showed increased râles over the chest posteriorly, the breath was labored, and there was a frequent harrassing cough. The child seemed quite sick, and a diagnosis of bronchopneumonia was made. On March 5 the von Pirquet was again negative, and on the 7th it was noted that the lungs were clear. On the day of entrance the red blood cells

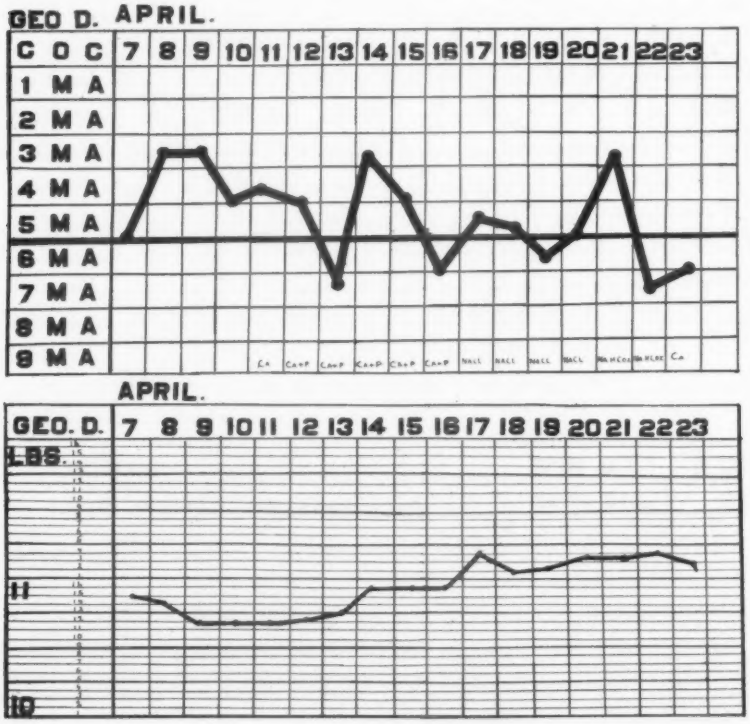


Fig. 6B.—Record of George D. (Case 6), aged 8 months. Second period. Upper division of chart shows the effect on electrical irritability produced by sodium bicarbonate and potassium citrate alternated with calcium lactate. Lower part of chart shows variation of weight for the corresponding period.

numbered 5,820,000, white cells 27,450, and the hemoglobin 85 per cent. A throat culture was negative for diphtheria and a urine analysis was negative. On March 3 the leukocyte count was 18,500, with a differential count of 61 per cent. polymorphonuclears, 31 per cent. small lymphocytes, and 1 per cent. basophils. From the time of entrance, when the child weighed 10 pounds 8 ounces, until March 22, when the child weighed 11 pounds 6 ounces, the weight was irregularly upward. On the day of exit, April 23, the child weighed 11 pounds 1 ounce. The temperature on the whole was normal; on February 21, 22 and 23 there was a slight fever, running as high as 101.8, when the child

developed a slight cold. The other febrile period was that which occurred during the attack of bronchopneumonia, which was at its height on March 4. With these exceptions the temperature was within normal limits, possibly rising to 100 at times. Table 1 is a record of the electrical irritability, together with laryngospasm.

TABLE 1.—Record of Electrical Irritability of George D., Case 6

Date, 1916	Dosage	Irritability, K.O.C., Ma.	Symptoms
2/15		1.5	Laryngospasm
	No medicine		
2/16		3.5	Laryngospasm
2/17		2.75	Laryngospasm
2/18		4.5	Laryngospasm
2/19		4.5	Laryngospasm
	$NaHCO_3$ 10 gr. every 2 hr.		
2/20		3.8	Laryngospasm
2/21		1.5	Laryngospasm
	Ca Lactate 15 gr. every 4 hr.		
2/22		6.5	Laryngospasm not so marked
	No medicine		
2/23		3.0	Pharyngitis
2/24		5.0	
	K. Citrate 10 gr. every 2 hr.		
2/25		2.75	Marked laryngospasm
	Ca Lactate		
2/26		4	No laryngospasm
2/27		4	No laryngospasm
2/28		3.5	Laryngospasm
2/29		5.0	Some laryngospasm
	K		
3/1		3.5	Marked laryngospasm
3/2		2.25	Marked laryngospasm
	No medicine		
3/3		3.0	Marked laryngospasm
4/7		5	
4/8		2½	Slight laryngospasm
4/9		2½	Laryngospasm
	Ca		
4/10		4	Laryngospasm
4/11		3.5	No laryngospasm
	Ca and P*		
4/12		4.0	No laryngospasm
4/13		over 5	No laryngospasm
4/14		2.5	No laryngospasm
4/15		4.0	Slight laryngospasm
4/16		6	No laryngospasm
	NaCl 10 gr. every 2 hr.		
4/17		4.25	No laryngospasm
4/18		4.5	No laryngospasm
4/19		5.5	No laryngospasm
4/20		5	No laryngospasm
	Na bicarbonate		
4/21		3.5	No laryngospasm
4/22		6.5	No laryngospasm
	Ca		
4/23		6	No laryngospasm

* Phosphorus was given in the form of cod liver oil and phosphorus (1/120 per cent.) 1 c.c. in each bottle of food.

CONTROL CASES

In order to see whether it would be possible to produce increased electrical reactions by the addition of sodium and potassium on persons who had never at any time shown increased electrical irritability and gave no history of spasmophilia, three children were tested, Mary P., aged 4 months, Annie R., aged 9 months, and Howard M., aged 18 months.

On January 6 in the case of Mary P., the electrical irritability was taken and was found to be, cathodal opening contraction equal to 10.5 ma. The child was given 10 grains of sodium bicarbonate, and 10 grains of potassium citrate every two hours, and on the 7th the electrical irritability was found to be 8 ma., on the eighth, 7, and on the 9th, 8 ma.

In the case of Annie R., Jan. 7, 1916, the cathodal opening contraction equaled 7 ma. Sodium bicarbonate and potassium citrate, 10 grains each were given every two hours for the next three days, with the result that in each instance the irritability remained over 5 ma.

In the case of Howard M., on the 7th and 8th the cathodal opening contraction was found to be over 5 ma. On the 8th the child was given 10 grains each of sodium bicarbonate and potassium citrate, without any influence on the electrical irritability. This was discontinued on the next day.

ACROCEPHALY

WITH A REPORT OF TWO CASES *

PHILIP LEWIN, M.D.
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Acrocephaly, or tower head, is the term applied to that syndrome consisting of a dome-shaped skull, with characteristic Roentgen-ray findings, exophthalmos and optic nerve changes, associated with some minor abnormalities, such as a high, arched palate and deformities of the hands or feet. Acrocephaly is synonymous with *thurmschädel, Spitzkopf,* steeple head, turret skull, *turritum caput, tête à la thersite.* When combined with deformities of the hands or feet the name acrocephalosyndactilysm is applied. Previous to 1911 Fletcher[1] found there had been reported between eighty and ninety cases. Von Graefe[2] in 1866 first definitely recognized and described the condition. Since then Michel,[3] J. Hirschberg,[4] Enslin,[5] Patry[6] and others have reported cases.

The etiology is obscure. The most probable cause is a premature ossification of the cranial sutures, but the underlying cause is unknown. There is not even a good theory. Syphilis does not seem to play an important part. In most of the reported cases the patients had had measles, but that is evidently not significant. Race does not predispose. Rickets has been found in some and absent in others. Males predominate in the reported cases. Heredity might play a rôle. J. Hirschberg reports a patient whose maternal grandfather was similarly affected. Weiss and Brugger mention two oxycephalic brothers seen by Oeller. Hanotte[8] states that Hamy saw two oxycephalic sisters. Fletcher reports a patient whose mother had a malformed head, exophthalmos and defective vision.

The malformation has been ascribed to intrauterine meningitis, which is supposed to cause early union of the sutures. Almond's[9]

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* Submitted for publication July 21, 1916.

1. Fletcher: Quart. Jour. Med., 1910-1911, **4,** 385.
2. Von Graefe: Arch. f. Ophth., 1866, **12,** Part 2, p. 114.
3. Michel: Arch. f. Heilkunde, 1873, **14,** 39.
4. Hirschberg: Centralb. f. Augenheilk., 1883, **7,** 1.
5. Enslin: Ophthalmoscope, 1904, **2,** 233.
6. Patry: Thèse de Paris, 1905; Recueil d'ophthal., Paris, 1906, Series 3, **28,** 156, 158; Ann. d'oculistique, Paris, 1906, **135,** 314.
7. Weiss and Brugger: Arch. Ophth., 1895, **24,** 55.
8. Hanotte: Thèse de Paris, 1898.
9. Almond: Alienist and Neurol., 1910, **31,** 487; Bristol Med.-Chir. Jour., **28,** 118, 1910, p. 1377.

patient cut two teeth before 3 months and sixteen before 1 year. He considers that the early appearance of teeth brings up the possibility of some hyperactivity of the osteoplastic tissue. Early union of sutures, especially coronal and sagittal, leads in some cases to microcephalic oxycephaly. In some cases, as in Almond's, some of the fontanels and sutures, the points of weakest resistance, apparently have yielded to increased pressure put on them, and this has led to the formation of encephaloceles (Fig. 3). The malformation of the orbit is generally supposed to be due to synostoses, affecting the base of the skull. Whether the narrowing of the optic canal is due to pressure downward and forward of the superior orbital plate, or whether the atrophy of the optic nerve is first caused by intracranial pressure, and the narrow optic canal is simply a lack of development corresponding to the small size of the nerve, is a matter of dispute.

Very few cases have been recorded with postmortem examination. H. Power[10] reports a full-term child brought to the hospital when thirty-six hours old, who died within thirty days. It was a typical case. The postmortem examination was as follows:

> Sagittal section was made through the vertical meridian of the right cornea. The orbit was extremely small, the entire depth being 2.5 cm. from the inferior border to the optic foramen. The floor of the orbit was horizontal, but the roof was almost vertical in position; it was formed mainly by the lesser wing of the sphenoid behind, and by a small portion of the orbital plate of the frontal bone in front. This roof was directed upward and forward at an angle of more than 45 degrees and was continuous with the vertical plane of the frontal bone, into which it passed with only a small projection to mark the orbital edge. A perpendicular line from the front of the vertical portion of the frontal bone fell entirely behind the globe. The whole orbit was too small to receive the globe of the eye. From its entrance at the optic foramen the nerve ascended sharply, and remained in close relation with the roof of the orbit till it bent downward to enter the sclerotic. The height of the orbit at its extreme anterior part was 32 mm., that of the normal skull for this age being 20 mm., so that the orbit was too wide at its opening and too shallow from before backward.
>
> The head was prolonged upward into a blunt cone; the result of this was to change the normal position of the convolutions of the brain, the frontal convolution and corpus callosum being perpendicular in direction.
>
> The anterior fontanel was present and open.

The striking features of a case are the deformity of the skull and the exophthalmos. For characteristic deformity of the skull see Figure 3. The exophthalmos may be extreme. Vision may be unaffected or totally destroyed. Optic atrophy is the most constant ophthalmologic finding. The disks are usually grayish, bluish or ivory with irregular edges, the arteries thin, the veins dilated and tortuous. Choked disks are present in some cases. In forty-two cases Enslin found the atrophy was postneuritic in thirty-six; in two it was regarded as primary.

10. Power, H.: Tr. Ophth. Soc. United Kingdom, 1894, **24**, 212.

Friedenwald[11] found postneuritic atrophy in nine of twelve cases. Occasionally there are pigmentary changes in the retina near the disk. Myopia is common.

There is usually a high-arched palate. In Almond's case it was impossible for the finger tip to reach the apex of the arch.

The Roentgen-ray findings are definite and characteristic. There is dimpling of the inner table of the skull (Figs. 3, 4 and 7).

The mentality may or may not be affected. Potts[12] states that in examining thousands of mentally defective patients he met with only two cases of acrocephaly. Hearing is usually unaffected, taste rarely affected. Meltzer found smell completely lost in twelve out of twenty cases. Headache may be frontal, vertical or occipital. Vertigo may or may not be present. The hairy scalp is frequently raised above the normal level, although the writer has seen striking examples of that condition with no other sign of acrocephaly. Because of the exophthalmos which is present in all marked cases there is failure of closure of the lids, with lacrymation and conjunctivitis.

Dislocation of the eyeball is not uncommon. Almond reports a case of a child in whom dislocation of either eyeball occurred occasionally when the child cried. Divergent strabismus is frequent and nystagmus is found in the majority of cases.

The thumbs may be flattened. There are all grades and kinds of associated abnormalities of the hands and feet. Gadelius[13] reports five cases with syndactylism. Poor extension of the elbows and shoulders has been noted.

There is frequently deflection of the nose. The complexion may be muddy. The patient is usually a mouth breather, and early dental caries has been noted in many cases.

CASE 1.—E. S., a white girl, 14 years of age, was admitted to Wesley Memorial Hospital on the service of Dr. Kanavel, having been referred by Dr. Patillo. The history, as I obtained it from the mother, showed that the girl was brought to the hospital because of (1) blindness, (2) weakness and small size of right arm, and (3) enlargement of the head. The early history showed that the patient had been a full-term baby, born without the aid of forceps. Her mother was in good health during the pregnancy, and although she was in labor only six hours she says it was a "hard labor." The child was born two hours after the membranes had ruptured. The mother was given chloroform. There was no asphyxia neonatorum. The child's head was normal in size and shape. She was breast fed for one year. She was the tenth child in a family of thirteen children.

She was perfectly well until she was 3 months of age, when she became ill. The trouble seemed to be "all in her head, because she was always rubbing her head and scratching her ears." There were no convulsions,

11. Friedenwald: Am. Jour. Med. Sc., 1898, **55,** 529; Proc. Roy. Soc. Med., Child. Sec., 1909, **2,** 277; ibid., Clinic. Sec., 1909, **2,** 115.

12. Potts: Rep. Soc. for Study of Dis. in Child., London, 1908, **8,** 407.

13. Gadelius, Bror: Nord. med. Ark., 1915, Division 2, **48,** 1-30.

opisthotonos, rigidities, or cough. There was a moderately high fever. The child was sick about two weeks and thenceforth "always seemed to have a headache." There was no epidemic of any disease at this time.

When 5 months old, for no apparent reason "her eyes gradually began to bulge and her head seemed to get large on top." At 5 or 6 months she had a tooth and at 12 months had ten. She sat up at 6 or 7 months and could walk and talk at 1 year. Until 18 months old she could walk and play like other children, but after that time her mother noticed that she could not see well. She would reach for objects and miss them. If she were given an object she would have to bring it close to her eyes in order to see it. Both eyes seemed to be affected simultaneously and to the same degree. At the 19th month her mother thought she could not see at all. Her ears never caused trouble, except when she caught cold, at which times she was slightly deaf.

At the age of 3 years she was taken sick with four or five convulsions, one of which was severe. The attack lasted two weeks, at the end of which

Figure 1

Figure 2

Figs. 1 and 2.—Two views of author's patient, Case 1.

time she was as well as previously, except for diminishing size and strength of the right arm as compared with the left

The headaches occurred frequently until a few years before entrance. The weak spells caused her to fall down and when picked up she was limp "as a rag." There was no foaming at the mouth or biting of the tongue. At first the spells occurred once a week, but she had had none for three years. There was no vomiting.

Following this illness and until two years before entrance, she had involuntary defecation and incontinence of urine, but at the time of entrance she had no trouble in that respect. She has always had a good memory. She has always been constipated.

At present there is no headache, she has control of the sphincters. There are no convulsions or rigidities. She can walk and talk, but does not know whether or not the sun is shining.

Menstruation began at 13 years, regular monthly type, with a duration of

four days. The flow was moderate in amount, and there was no dysmenorrhea or metrorrhagia.

The mother and father were well and never had been seriously ill. The maternal grandparents were well at 70 and 72. The paternal grandfather died of pneumonia, the grandmother of "old age."

There is no similar case in the family. The mother had thirteen live children, of which the patient was number ten. Four are dead: two of pneu-

Fig. 3.—Roentgenogram of cranium, Case 1; anteroposterior view

monia at 8 and 16 weeks of age, one being the eighth child; one of diphtheria at 21 weeks, being the second child; one lived three or four days, an eight months' pregnancy; a full-term pregnancy, the ninth, resulted in a dead baby. Nine children are living, the other eight are very well. The oldest, a woman of 30, has one child who is well. She had a seven months' spontaneous miscarriage. There are no other daughters married. Two sons are married; their wives have never been pregnant. All the children walked and talked early. The mother denies any evidence of specific disease in herself or husband.

Physical examination was made by Dr. Kanavel, Oct. 1, 1915. The patient proved to be a fairly well-nourished girl of normal size for fourteen years of age. There was rounded kyphosis in the upper portion of spine, with slight lordosis, probably postural in origin. The patient was in the habit of sitting with the mouth open and the lower jaw dropped. The lower lip was thick. When mouth was closed the lower jaw projected 1 cm. above the upper jaw. The nose was turned slightly to the right. There was marked exophthalmos of both eyes, especially the right. There was divergent strabismus when eyes were at rest. On the slightest tension there was marked double nystagmus.

There was marked anteroposterior nondevelopment and excessive vertical development of the cranium (Figs. 1, 2, 3 and 4). The protuberance along the

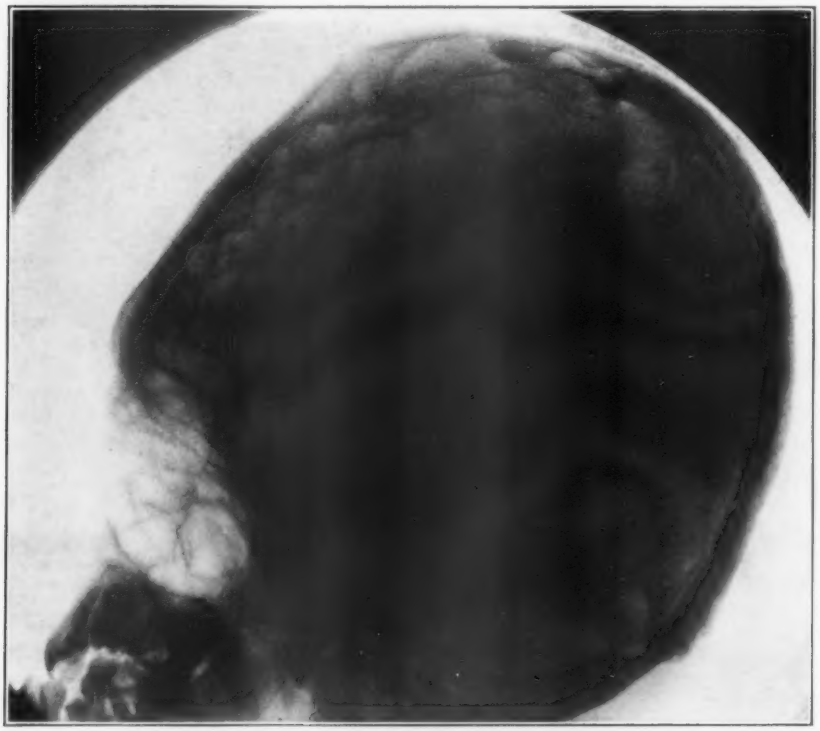

Fig. 4.—Lateral view of skull in Case 1, showing hernia cerebri.

median line was 7.5 cm. long and 5 cm. wide. On the anterolateral aspect of this protuberance a semifluctuant sensation could be elicited. This was a hernia cerebri and was tender (Fig. 3). Otherwise the body was symmetrical and there were no gross deformities.

Measurements taken showed the circumference of the head around the occipital protuberance and glabellum to be 48 cm.; the occipitoglabellum diameter over the vertex, 32 cm.; auditory meatus to auditory meatus (around the head). 66 cm.; and the mentooccipital diameter, 60 cm.

The child habitually protruded the tongue to the right, but showed no marked evidence of paralysis. She swallowed without difficulty. The facial nerve was intact. It was impossible to estimate accurately the power of the

ocular muscles, but the patient did not turn the eyeballs inward. The eccentric pupil was at the upper inner quadrant of each eyeball.

Sensation over the body was normal. The muscular sense was normal except in the right arm. The knee reflexes were normal. There were no Babinski, Oppenheim, Gordon or ankle clonus. There was apparent loss of the stereognostic sense in the right hand.

The lungs and the heart were normal. The right arm was smaller and weaker than the left.

Examination of eyes by Dr. Patillo showed the pupils dilated, with no response to light. There was lateral nystagmus. Light perception was absent, due to a double primary optic atrophy.

Examination of the ears by Dr. J. Gordon Wilson revealed a chronic suppurative otitis media on the left side. There was no other gross pathology of the sphenoid bones.

Temperature ranged from 97.6 to 98.6, the pulse from 76 to 104, usually about 90. The respirations varied from 18 to 24.

Blood examination, made Sept. 27, 1915, showed 4,952,000 red blood cells, 15,800 white blood cells, lymphocytes 22 per cent., large mononuclears and transitionals 5 per cent., polymorphonuclear neutrophils 72 per cent., polymorphonuclear basophils 1 per cent., hemoglobin 98 per cent. (Dare). On September 29 blood examination gave 5,656,000 red blood cells, 14,000 white blood cells, lymphocytes 22 per cent., polymorphonuclears 78 per cent., hemoglobin from 91 to 94 per cent. (Dare).

Three examinations of the urine each proved negative. An examination of the spinal fluid was made Oct. 2, 1915. The Wassermann reaction performed by Dr. Holmes proved negative. Spinal fluid examination made by Dr. A. L. Moody on Mrs. S., the patient's mother, on the same date, showed Nonne and Noguchi reactions both negative. The cell count was 5 per c.mm. The Lange test was negative.

Case 2.—W. McC., a colored boy, aged 6 years, entered St. Luke's Hospital on the service of Dr. H. W. Cheney (later transferred to Drs. F. X. Walls and J. Brennemann). The complaint, as given by the mother, was stiffness of neck, headache, bulging eyes and lateral retraction of the head. Two months before admission the boy began to have attacks of stiffness in the side and back of the neck. These attacks lasted from 1 p. m. till bedtime and were unilateral, but involved both sides at different times. Simultaneously his head began to lean toward the right. His trouble was exaggerated by "colds."

Previously he had been like the other children, but when these attacks began he acted "dopey." He had fever almost every afternoon. Headache usually began at 11 a. m. and continued until bedtime. The appetite was unaffected.

The eyes began to bulge when the boy was 5 or 6 months old, but his vision was apparently unaffected. The shape of his head had been unusual from birth. The date of closure of the anterior fontanel was unknown. The boy was a mouth breather. He was taken out of school because of headaches, which were promptly alleviated. The boy had measles at 4 years and mumps at 5, but no other illness.

He had a sister who at 6 years of age started to have similar trouble, that is, stiffness of the neck with retraction of the head. She died of tubercular meningitis three months later. There are two other sisters, one well, the other, 14 years old, has been in the Municipal Tuberculosis Sanitarium for two months. She has tubercular cervical adenitis. The father died of pulmonary tuberculosis six years before. The mother was in good health.

The patient was a negro boy about 6 years of age. The development and nutrition were good. There was no marked evidence of rickets and no rash. The head was large, of the typical shape of acrocephaly. It came up to a point like a dome (Figs. 5 and 6). The scalp was negative. The fontanels were

closed. Measurement showed the diameters to be as follows: suboccipitobregma 15 cm., suboccipitofrontal 17 cm., occipitofrontal 17.5 cm., occipitomental 22 cm., biparietal 12.5 cm., bisacromial 25 cm. The circumferences were as follows: Occipitofrontal 50.5 cm., suboccipitofrontal 50 cm., bisacromial 74 cm. The distance between the external auditory meati over the dome was 36 cm.; from the inion to the nasion over the dome 36 cm. From the external auditory meatus to the highest point of the skull the distance was 17.5 cm. The circumference from the chin to the subocciput was 47 cm.

The head was drawn to the right. There was marked exophthalmos. When the boy closed his eyes the sclera was exposed for a space one-eighth of an inch wide. This was more marked on the right side. The ears and nose were normal, the throat hyperemic, the teeth good, palate very highly arched. The neck was not rigid. The cervical glands were shotty.

There was a slight rosary, but the heart and lungs were normal. The abdomen was large (pot-belly) but there was no tenderness, rigidity, or enlarge-

Figure 5

Figure 6

Figs. 5 and 6.—Two photographs of colored boy, author's Case 2, as described in text.

ment of the viscera. The extremities showed slight evidence of rickets. The reflexes were exaggerated.

On Jan. 6, 1916, examination of the eyes was made by Dr. Brawley. The primary optic atrophy was not far advanced and the vessels had not as yet shrunken. The disk was white and vertically oval; with the ophthalmoscope the disk was best seen, left eye with + 3, right eye with + 4.

The urine was negative; the white blood cells 14,800. A roentgenogram made by Dr. C. L. Moir, Dec. 24, 1915, showed a marked case of acrocephaly (Fig. 7). Dec. 21, 1915, the Wassermann reaction was negative, performed by Dr. Leila Jackson. The highest temperature was 100.4. The patient runs a slight afternoon fever of about 99.4. There are no night sweats or cough. The appetite is good. The report of Mrs. Bersch, kindergarten teacher, shows that the mentality is good. He can be taught as easily as other children of his age and race.

Because of failure of the lids completely to cover the eyes the boy developed an orbital conjunctivitis. While that part of the treatment consisting of boric solution irrigation was being done, on one occasion the eyeball became dislocated from simply inverting the lid. It was replaced with little difficulty.

The diagnosis in a well-developed case of acrecephaly is easy. A good history is of value. Physical examination, with careful ophthalmoscopic study, is usually conclusive, and the Roentgen ray will clear up any doubtful cases. The prognosis as to life is good, as to improvement very poor.

There is no satisfactory treatment. In 1913 Schlosser[14] reported to the German Surgical Congress his operation on two patients. It consists in turning down a skin and bony flap on the forehead, then

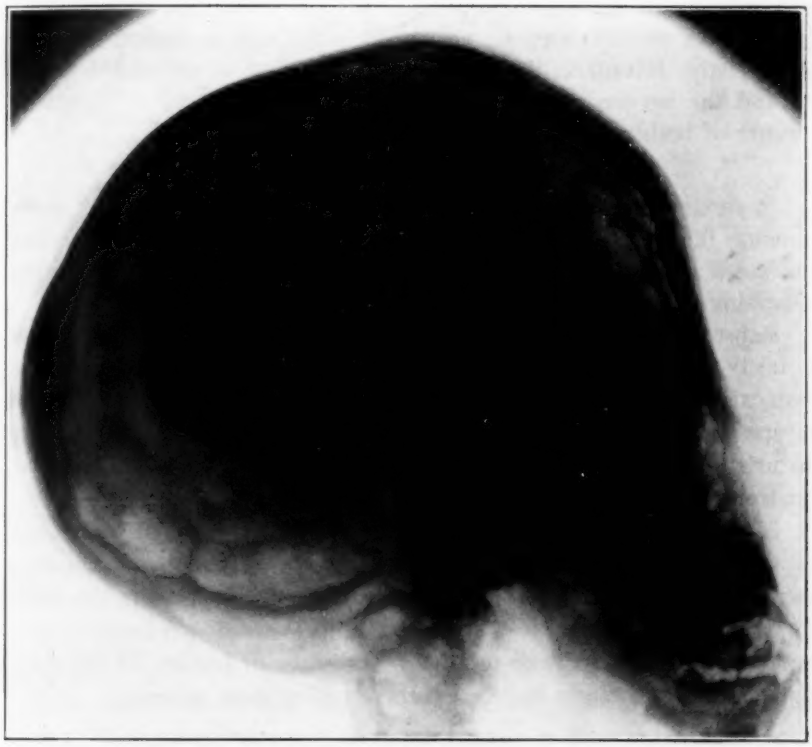

Fig. 7.—Roentgenogram of head, author's Case 2; lateral view.

the dura and frontal lobe are lifted up and the superior portion of the optic canal is removed with a chisel. He performed the operation on two children with practically no visual improvement whatever. Treatment with glands of internal secretion has been suggested, but there are no data on the subject.

Gadelius[13] and Davis[15] report excellent cases of acrocephalosyndac-

14. Schlosser: Deutsche Gesellschaft für Chirurgie, Germ. Surg. Cong., 1913; Arch. f. Ophth., 1904, **58,** 151, A673.

15. Davis, Ben: Am. Jour. Dis. Child., 1915, **9,** 446.

tylism. The former shows photographs and roentgenograms of cases. One patient had fusion of first three fingers of both hands; another had no thumbs and the fingers were fused into one mass with practicaly total absence of metacarpals; another had thumbs, but the fingers were fused into one mass. The foot had a similar deformity.

Stein[16] reported an interesting case with mentality and fundi unaffected, but with typical dimpling of the inner table of the skull. The condition was unknown to the patient. She sought advice for palpatation, dyspnea, cough and headaches, all of which were accounted for by a mitral stenosis.

Fenton's patient was 40 years old. He was a typical case of acrocephaly. His mentality was normal, in spite of an extreme deformity and the severest ocular complications. He suffered a traumatic rupture of both eyes.

SUMMARY

In summarizing I desire to say that these cases are probably more common than is generally believed. The diagnosis is very easy when one has a good history, makes careful physical examination, including ophthalmoscopic study, and has good roentgenograms.

Before we can have a rational treatment we must first establish a fairly definite etiology. To ascribe the condition to premature ossification of certain sutures sounds well, but what causes the sutures to ossify prematurely? Is acrocephaly a syndrome due to some disturbance of one gland of internal secretion, or is it a pluriglandular syndrome?

It seems reasonable that the treatment should proceed along one or two lines, namely, first gland, or extracts of glands, of internal secretion, second, when symptoms of intra-ocular pressure or optic compression are found, if a skilled decompression is performed, with removal, either partially or totally, of the superior portion of the optic canal, some hope might be offered these unfortunate patients.

In conclusion I wish to express my appreciation of the kindness of Drs. Kanavel, Cheney, Walls, and Brennemann in permitting me to report these cases, and to those whose names are mentioned in the paper, my sincere thanks.

30 North Michigan Avenue.

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THE EXCRETION OF SODIUM CHLORID SOLUTION , INJECTED SUBCUTANEOUSLY *

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Hypodermoclysis as a means of replacing the loss of fluid which occurs in severe diarrhea, protracted vomiting or as a result of hemorrhage has been employed for a number of years with an increasing appreciation of its value in these conditions. Our studies of diarrheal stools showed great loss of salts, especially the more soluble ones, sustained in these intestinal conditions. It seemed to us, therefore, that benefit should result from the restitution not only of the water lost, but also of some of the salts themselves. The nature of the variations in weight after hypodermoclysis suggested that these were due to something more than simply a retention of the water injected. Moreover, in view of the necessity in many cases of repeating the injections, it was desirable to know exactly what the salt retention was. The observations which are included in this paper were undertaken to determine if any of the salt so given was retained, or how rapidly it was eliminated.

The solution employed was made from freshly distilled water and sterilized in the hypodermoclysis flask. This is an ordinary small-necked flask of about 250 c.c. capacity, fitted with a two-hole rubber stopper carrying short pieces of glass tubing, one of which is connected by rubber tubing with an ordinary hypodermic needle. The bottle containing the solution, heated to body temperature, is fastened, inverted, near the bed at a suitable height and kept sufficiently warm by being wrapped in a cloth. The needle is usually inserted in the back, preferably between the scapulae, and held in place by strips of adhesive plaster. The entire apparatus as well as the solution is sterilized and the injection is made with aseptic precautions.

Generally a physiologic salt solution was used; but in several instances a special solution, one suggested by Dr. Jacques Loeb, was employed as more nearly approximating the salt content of the blood than does a normal saline. The composition of this solution was sodium chlorid 0.86 gm., potassium chlorid 0.02 gm., calcium chlorid

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0.64 gm. (including water of crystallization), and distilled water 100 c.c.

In the cases here reported about 200 c.c. of the solution was allowed to run into the tissues. This usually required from one to three hours according to the degree of dehydration of the body of the infant, those most dehydrated taking up the solution most readily. Also, the first injections were taken up more rapidly than those given on succeeding days. The rate of absorption varied greatly, the time required for complete disappearance of the fluid from the site of injection ranging from four to twelve hours. The rate was slower in subsequent than in first injections.

Careful temperature records after injection were kept by Dr. C. B. Crawford of the resident staff in a large series of cases. A slight febrile reaction occurred in about one-fourth the children, even when the strictest precautions in preparing the solution were observed. The average temperature was about 101.5 F., though occasionally in susceptible infants temperatures as high as 103 were recorded. The rise of temperature commenced four or five hours after the beginning of the injection and continued on an average for six hours.

Whether the injection of the solution affects the volume of the urine and the number and character of the stools is a question regarding which there has been very little positive knowledge. Nor have many observations been made on the elimination of the salts after hypodermoclysis.

The literature of the last ten years contains numerous contributions on sodium chlorid metabolism. The point which has received most attention is the influence of salt on the body temperature. Besides this there have been a number of studies on the effect of the salt intake on the body weight. Several papers have discussed the difference in the effect of salt given by mouth and that given by hypodermic injection. A number of metabolism studies have been made on adults after salt injections, but we have been able to find only a single paper which gives metabolism figures in infants after salt injections.

Friberger[1] reports on five infants (four of whom were healthy) who received from 60 to 80 c.c. of a normal salt solution hypodermically. He found some increase in the salt excretion on the first day; the maximum excretion, the second day, and an excessive excretion continuing for two or three days longer. These observations, as far as they go, agree with our findings; but the number of cases is small, the amount injected was much less than in the cases reported here, and all of his observations, with but one exception, were on healthy children.

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1. Friberger: A Study of So-Called Salt Fever and Chlorin Excretion in Infants, Arch. f. Kinderh., 1910, **53,** 17.

The series of investigations here reported was made with the view of determining the effect of hypodermoclysis on salt metabolism, and as far as possible on water metabolism in infants. For the last three years hypodermoclysis has been in daily use at the Babies' Hospital in a wide variety of conditions and has been given to many hundreds of children. Out of this number, twenty-four have been selected for special study. Of these, nine represent the type for whom hypodermoclysis is most frequently employed therapeutically; while fifteen, who may be considered normal children, were studied as controls. The age, food and general condition of these children are given in Table 1.

In eleven of the children the special salt solution mentioned was used; in the others the ordinary physiologic salt solution. The use of the Loeb solution was discontinued, because no clinical difference or unusual variations in metabolism could be discovered with its use.

In every instance the child was placed in the metabolism bed and total twenty-four hours' urine and feces were collected for one or two days before the salt solution was injected, and as a rule for three days after the injection. It would doubtless have been better to have had longer periods of observation, but it commonly happened that after five or six days conditions rendered it desirable to make changes in the treatment, thus necessitating comparatively short metabolism periods. It is also to be regretted that the intake by mouth unavoidably varied so much in some of the cases. It was the desire to make the observations under natural conditions and no attempt was made to force food when it was refused. The injection was always given at the beginning of a metabolism day.

In the first eleven cases complete metabolism studies were made of water, nitrogen, total ash, calcium oxid, magnesium oxid, phosphorus pentoxid, chlorin, potassium oxid and sodium oxid. In the remaining thirteen cases, however, only water and chlorin were determined. The separate determination of sodium oxid was omitted, being laborious and apparently of no importance for our purposes. If the sodium chlorid equivalent is desired it is obtained by multiplying the figure for chlorin by 1.648. In speaking of a water balance, it must be kept in mind that the water lost in the respiration and perspiration was not considered.

The methods used are the same as those reported in former papers from these laboratories.[2]

The only salt which could be expected to show a marked difference in the elimination after hypodermoclysis, even when the Loeb solution is used, is sodium chlorid, as this is the only one injected in any con-

2. Holt, Courtney and Fales: Chemical Composition of Diarrheal as Compared with Normal Stools in Infants. Am. Jour. Dis. Child., 1915, **9**, 213.

TABLE 1.—Age, Food and General Condition of Infants Used in Investigations of Effect of Hypodermoclysis on Salt and Water Metabolism

Name	Age,	Initial Weight, Gm.	Condition	Food	Stools
1. L. O.	10¼	5,285	Previously normal, but developing diarrhea	Protein milk	Watery and semiformed with fat-curds and mcus, yellow-brown and green
2. R. S.	12	7,143	Normal.....	Whole milk, 2 eggs, 1 oz. beef juice.....	Brown, soft, formed
3. H. R.	6	5,651	Normal, except for rickets	Fat 2.2, carbohydrate 6, protein 2, including dextrimaltose	Partly constipated, hard, brown; partly pasty, granular, with fat-curds and mucus
4 Jos. M. ..	17	10,305	Normal.....	Whole milk, 2 oz. cereal, 2 eggs.....	Pasty, semiformed with fat-curds and mucus, brownish yellow; later becoming watery and fermentative
5 Jos. S. ...	17½	9,615	Normal, after eczema	⅔ milk, ⅓ barley water, ⅔ water; 2 eggs; ½ oz. scraped beef	Thin, with mucus, yellow-brown
6. H. B.	13	6,998	Normal.....	Whole milk, cereal, bread, 12 c.c. malt soup extract	Partly formed, constipated, brown; partly pasty, granular with mucus and fat-curds, greenish brown
7. S. J.	9	4,897	Normal, but developed diarrhea during period	Fat 2.4, sugar 3, Protein 2.2, from condensed milk; barley flour 45 c.c.; cane sugar 15 c.c.	Partly formed, partly pasty; later becoming fermentative, with curds
8. T. M.	13¼	7,749	Normal.....	Whole milk, 2 oz. cereal.....	Partly pasty; partly watery, with fat curds, greenish
9. J. T.	9	6,650	Normal, except for rickets	Fat 3, sugar 4, protein 2.8; barley flour 45 c.c. ..	Partly constipated; partly softer, semiformed; brown
10. J. M.	11	7,359	Convalescent from scurvy	Skimmed milk; orange juice.....	Partly formed; partly pasty and watery, with fat-curds; yellow and gray
11. W. C.....	6	7,179	Normal.....	Fat 2.4, sugar 4, protein 2.2; ½ egg.....	Mostly formed; partly pasty, with mucus; yellow-brown and yellow

12. P. D., 1..	3½	3,686	Convalescent from diarrhea and vomiting	Protein milk	Partly formed; partly watery, with fat-curds; greenish yellow and gray
13. P. D., 2..	7½	4,761	Normal.....	Fat 2.8, sugar 4, protein 2.6; ¾ oz. malt soup extract; 75 c.c. uncooked barley flour	Soft, formed, brown
14. M. di G.	5¼	4,305	Normal.....	Fat 2, sugar 2.5 protein 1.8, from condensed milk; imperial granum 30 c.c.; cane sugar 15 c.c.	Partly pasty, partly watery, with fat-curds and mucus; pale yellowish green
15. P. M.	3½	3,670	Normal.....	Protein milk, 5 feedings; and 2 feedings, fat 1.6, sugar 5, protein 1.4; 30 c.c. imperial granum in protein	Partly formed, brown; partly pasty and watery, greenish
1. I. G.	2½	2,814	Losing weight.....	Fat 1.8, sugar 2.25, protein 1.6, from condensed milk; barley flour 30 c.c.; cane sugar 8 c.c.	Loose, pasty, fermentative, with curds and mucus, greenish yellow
2. E. K.	6	3,765	Vomiting and losing weight	Fat 1.2, sugar 4, protein 2.2.....	Hard, formed, smooth, gray; later becoming softer, semiformed
3. J. C.	3½	4,358	Diarrhea.....	Protein milk	Watery, with fat-curds and mucus, greenish yellow
4 T. M.	2¼	2,855	Marasmus with diarrhea	Protein milk, barley water.....	Very watery, fermentative, with fat-curds and mucus, yellowish green
5. V. V.	2¼	2,953	Vomiting and losing weight	Fat 1.6, sugar 5, protein 2.2.....	Partly pasty, partly watery, with fat-curds and mucus; greenish yellow
6. J. B.	4½	3,716	Marasmus with diarrhea	Protein milk; 30 c.c. dextrimaltose.....	Very watery, with fat-curds and mucus
7. L. M.	5	4,432	Diarrhea and vomiting	Protein milk	Watery, with curds and mucus, greenish yellow; later becoming pasty and gray
8 J. P.	8	6,778	Diarrhea and vomiting	Protein milk; albumin water.....	Watery, with fat-curds and mucus, yellowish green and brown
9. C. B. ...	2	2,759	Marasmus with diarrhea	Protein milk; barley water; breast milk.....	Very watery, with fat-curds and mucus, greenish

TABLE 2.—METABOLISM STUDIES OF WATER—

Name	Period	Water Balance, C.c.							Chlorin Bal., Gm.	
		Intake by Mouth	Injected	Total Intake	Urine	Feces	Total Excretion	Retained	Intake by Mouth	Injected
1. L. O.	Before injection (daily aver.)	1,231	.....	1,231	470	187	657	574	0.8773	.....
	1st day after	1,149	193	1,342	450	358	808	534	0.6199	1.351
2. R. S.	Before injection	921	.....	921	300	24	324	597	1.1726	.....
	1st day after	1,113	198	1,311	577	38	615	696	1.1808	1.1286
3. H. R.	Before injection	1,015	.....	1,015	620	13	633	382	0.7046	.....
	1st day after	1,131	212	1,343	700	63	763	580	0.7192	1.1872
	2d day after	1,121	.....	1,121	795	39	834	287	0.7262	.....
4 Jos. M.	Before injection	771	.....	771	255	65	320	451	1.7956	.....
	1st day after	400	230	630	410	72	482	148	0.925	2.852
	2d day after	521	.....	521	385	268	653	—132	1.0802	.....
5. Jos. S.	Before injection	625	.....	625	140	137	277	348	1.0203	.....
	1st day after	649	235	884	220	93	313	571	1.0678	1.2925
	2d day after	695	.....	695	330	154	484	211	0.7807	.....
6. H. B.	Before injection (daily aver.)	1,035	.....	1,035	660	50	710	325	1.6876	.....
	1st day after	980	160	1,140	720	99	819	321	1.6265	0.8840
	2d day after	1,005	.....	1,005	478	73	551	454	1.6543	.....
	3d day after	1,010	.....	1,010	550	59	609	401	1.6598	.....
7. S. J.	Before injection (daily aver.)	955	.....	955	305	81	386	569	0.835	.....
	1st day after	1,055	180	1,235	630	191	821	414	0.923	0.994
	2d day after	1,105	.....	1,105	420	200	620	485	0.966	.....
	3d day after	1,130	.....	1,130	290	284	574	556	0.988	.....
8. T. M.	Before injection	920	.....	920	175	194	369	551	1.3635	.....
	1st day after	845	209	1,054	505	170	475	579	1.2523	1.0805
	2d day after	830	.....	830	380	149	529	301	1.2301	.....
	3d day after	970	.....	970	378	135	513	457	1.4375	.....
9. J. T.	Before injection (daily aver.)	858	.....	858	248	36	284	574	0.628	.....
	1st day after	845	190	1,035	435	27	462	573	0.619	1.0377
	2d day after	855	.....	855	500	29	529	326	0.625	.....
	3d day after	800	.....	800	480	28	508	292	0.586	.....
10. J. M.	Before injection	952	.....	952	285	68	353	599	0.8480	.....
	1st day after	1,030	206	1,236	235	89	324	912	0.7920	1.5553
	2d day after	1,123	.....	1,123	410	82	492	631	0.8949	.....
	3d day after	962	.....	962	400	75	475	487	0.8546	.....
11. W. C.	Before injection	865	.....	865	630	76	706	159	0.5420	.....
	1st day after	1,065	215	1,280	700	0	700	580	0.5280	1.1610
	2d day after	1,125	.....	1,125	830	48	878	247	0.4716	.....
	3d day after	1,130	.....	1,130	790	21	811	319	0.5744	.....

Chlorin Balance, Gm.					Summary
Total Intake	Urine	Feces	Total Excretion	Retained	
0.8773	0.0086	0.4678	0.4764	0.4009	All injected chlorin and water were eliminated in 24 hours; the water mainly through the feces, the chlorin equally in urine and feces
1.0709	0.5175	1.0498	1.5673	0.4036	
1.1726	0.492	0.0117	0.5037	0.6689	More than the amount of injected chlorin was eliminated in 24 hours; not more than half the water; the increased excretion was practically all in the urine
2.3094	1.7577	0.0228	1.7805	0.5289	
0.7046	0.4464	0.0081	0.4545	0.2501	The elimination of injected water and chlorin was slightly greater in the second 24 hours than in the first; somewhat more than the amount of injected chlorin was lost in 48 hours, but only half the water. The increased chlorin excretion was mainly through the urine, the water in both urine and feces
1.9064	0.9932	0.0540	1.0472	0.8592	
0.7262	1.0922	0.0338	1.1260	—0.3998	
1.7056	1.3158	0.0939	1.4097	0.3859	The injected chlorin was eliminated largely through the urine, the greater part in the first 24 hours; the injected water also in the first 24 hours' urine and a large amount besides in the feces of the second 24 hours; much more than the amount of both water and chlorin injected lost in 48 hours
3.7770	2.7267	0.0272	2.7589	1.0231	
1.0802	1.8446	0.1898	2.0344	—0.9542	
1.0203	0.4928	0.2262	0.7190	0.3013	Nearly all the injected chlorin eliminated in the first 24 hours and greatly increased excretion for 36 hours longer (the period of observation); increased water elimination in the second 24 hours, but not all the injected water lost; the increased excretion was in the urine
2.3603	1.7795	0.1620	1.9415	0.4188	
0.7807	1.4100	0.0777	1.4877	—0.7070	
1.6876	1.6104	0.0256	1.6360	0.0516	All the injected water and chlorin eliminated, mainly in the urine of the first 24 hours, after which the excretion was greatly decreased from the normal; retention therefore increased
2.5105	2.5200	0.0552	2.5752	—0.0647	
1.6543	1.2650	0.0409	1.3059	0.3484	
1.6508	1.4410	0.0327	1.4737	0.1861	
0.835	0.5216	0.0451	0.5667	0.2683	All the injected water and chlorin eliminated in the first 24 hours, the water and most of the chlorin through the urine; further loss of both chlorin and water through the feces, but to an increasing diarrhea following hypodermoclysis; diarrhea possibly due to feeding of high carbohydrate
1.9170	1.4364	0.2480	1.6844	0.2326	
0.960	0.7182	0.2610	0.9792	—0.0132	
0.988	0.6560	0.3690	1.0250	—0.0370	
1.3035	0.6720	0.0287	0.7007	0.6028	Practically all the injected water and chlorin lost in the first 24 hours' urine; but increased excretion of both water and chlorin continued 48 hours longer, resulting in greatly reduced average daily retention; feces somewhat reduced in both water and chlorin
2.3328	1.6000	0.0190	1.6190	0.7138	
1.2301	1.3440	0.0167	1.3607	—0.1306	
1.4375	1.1760	0.0151	1.1911	0.2464	
0.628	0.4695	0.0267	0.4962	0.1318	All injected water eliminated in urine in the first 24 hours; but increased excretion continued during period of observation (three days); about half the injected chlorin eliminated in first 24 hours' urine; increased excretion continued through period of observation, but not quite all injected chlorin was lost in 72 hours
1.6567	1.0266	0.0164	1.0430	0.6137	
0.625	0.7000	0.0172	0.7172	—0.0922	
0.586	0.6000	0.0171	0.6171	—0.0311	
0.8480	0.4418	0.0140	0.4558	0.3922	No injected water eliminated; chlorin excreted in part the first day, the maximum amount on the third day; nearly all the increased excretion was through the urine, both water and chlorin in the feces being only slightly increased; part of the chlorin was retained at the end of the third day, though increased excretion was continued
2.3473	0.8037	0.0185	0.8222	1.5251	
0.8949	0.7134	0.0159	0.7293	0.1656	
0.8546	0.9000	0.0304	0.9304	—0.0758	
0.5420	0.3780	0.0685	0.4465	0.0955	No injected water eliminated during time of observation; feces decreased and urine not increased so much as the intake by mouth; more than the amount of injected chlorin was eliminated in three days, somewhat more on the second and third days than on the first; increased excretion entirely through the urine
1.6890	0.8536	0.0000	0.8536	0.8354	
0.4716	0.9482	0.0264	0.9746	—0.5030	
0.5744	0.9408	0.0086	0.9494	—0.3750	

TABLE 2.—METABOLISM STUDIES OF WATER AND—

Name	Period	Water Balance, C.c.							Chlorin Bal., Gm.	
		Intake by Mouth	Injected	Total Intake	Urine	Feces	Total Excretion	Retained	Intake by Mouth	Injected
12. P. D., 1.....	Before injection	651	.....	651	400	70	470	181	0.4626	.....
	1st day after....	806	196	1,002	405	37	442	560	0.5603	1.3720
	2d day after....	798	.....	798	400	90	490	308	0.4351	.....
	3d day after....	811	.....	811	335	67	402	409	0.4805	.....
13. P. D., 2.....	Before injection (daily aver.)	1,101	.....	1,101	617	28	645	456	0.7280	.....
	1st day after....	1,035	210	1,245	575	23	598	647	0.6940	1.1865
	2d day after....	1,006	.....	1,006	670	65	735	271	0.6940	.....
	3d day after....	1,065	.....	1,065	675	43	718	347	0.7160	.....
14. M. di G.	Before injection	895	.....	895	445	177	622	273	0.7151	.....
	1st day after....	875	144	1,019	495	125	620	399	0.7000	0.7546
	2d day after.... (2d injection)	930	206	1,136	725	159	884	252	0.7430	1.0712
	3d day after....	965	.....	965	480	101	581	384	0.7710	.....
	4th day after....	945	.....	945	390	148	538	407	0.7560	.....
15. P. M.	Before injection (daily aver.)	807	.. ..	807	535	25	560	247	0.5420	.....
	1st day after....	920	100	1,020	515	24	539	481	0.5199	0.700
	2d day after.... (2d injection)	804	200	1,004	700	30	730	274	0.4861	1.420
	3d day after....	902	.....	902	520	16	536	366	0.4231	.....
	4th day after....	938	.....	938	530	25	555	383	0.5489	.....

siderable amount. It is, therefore, to this and to the water that the attention was especially directed.

As already stated, with eleven of the children complete metabolism studies, both before and after injection, were made of calcium oxid, magnesium oxid, phosphorus pentoxid and potassium oxid, as well as of sodium oxid and chlorin; but except as regards sodium oxid and chlorin, the differences between the retention before and after hypodermoclysis were no greater than the variations ordinarily observed when no injection of salt has been given. Moreover, there was no uniformity in the elimination of calcium oxid, magnesium oxid, phosphorus pentoxid and potassium oxid after the injections; sometimes the retention was practically unchanged, at other times there was a slight increase in retention, and in still others a slight decrease. In view of the indefinite character of the results of this part of the observations, the tables for these constituents have not been included in this report.

—CHLORIN IN NORMAL CHILDREN—(*Continued*)

Chlorin Balance, Gm.					Summary
Total Intake	Urine	Feces	Total Excretion	Retained	
0.4626	0.0720	0.1634	0.2354	0.2272	No injected water eliminated during period of observation (three days); less than half the injected chlorin lost through the urine on the first day and successively smaller amounts on the second and third days; a large part of the injected chlorin retained at the end of the period of observation
1.9823	0.7047	0.0543	0.7590	1.1733	
0.4351	0.3600	0.1218	0.4818	−0.0467	
0.4805	0.2211	0.1463	0.3674	0.1131	
0.7280	0.555	0.0164	0.5714	0.1566	All of the injected water eliminated on the second and third days, chiefly through the urine; about half the injected chlorin excreted in the first day's urine and a smaller amount on the second day, with normal excretion on the third day, leaving a part not eliminated
1.8805	1.0439	0.0074	1.0613	0.8292	
0.6940	0.8945	0.0209	0.9154	−0.2214	
0.7160	0.5902	0.0141	0.6043	0.1117	
0.7151	0.3827	0.0567	0.4394	0.2757	Very little of the injected water lost on the first day; on the following day, after a second injection, there was excreted through the urine an amount equal to the second injection; on the third and fourth days excretion through both urine and feces was so reduced that in the period of observation an additional amount of water was retained about equal to the two injections. All the injected chlorin was eliminated, mostly through the urine, in the first three days, the largest amount on the second day; on the fourth day there was normal excretion in the urine, but increased chlorin in the feces
1.4546	0.8800	0.0861	0.9661	0.4885	
1.8142	1.4210	0.1093	1.5303	0.2839	
0.7710	0.6048	0.1113	0.7161	0.0549	
0.7560	0.3520	0.1641	0.5161	0.2399	
0.5420	0.3373	0.0197	0.3570	0.1850	No injected water was lost on the first day; on the following day, after a second injection, there was excreted through the urine an amount about equal to the second injection, but on the third and fourth days, excretion was so reduced that in the period of observation an additional amount was retained more than equal to the two injections. A small part of the injected chlorin was excreted through the urine on the first day, a much larger amount on the second day; on the third and fourth days excretion was little more than normal, so that in the period of observation a considerable part of the injected chlorin was retained
1.2199	0.5305	0.0243	0.5548	0.6651	
1.9061	1.3020	0.0337	1.3357	0.5704	
0.4231	0.3172	0.0354	0.3526	0.0705	
0.5489	0.4664	0.0233	0.4897	0.0592	

Tables 2 and 3 give the results of metabolism studies of water and chlorin in normal and abnormal children. The accompanying illustrations (Figs. 1 and 2) represent graphically some of the fairly typical cases.

Among the fifteen normal children, seven eliminated all the injected water during the period of observation — six in the first day and one in three days; five excreted a considerable part during the period of observation, that is, two or four days; and three lost none in three days. Of the injected chlorin, ten children lost the entire amount during the period of observation—six on the first day, two in two days and two in three days; five excreted part of the chlorin in the period of observation—three days or four days. In four cases the water loss and in five the chlorin loss for the whole period was considerably more than the amount injected. In three cases the water loss and in one the chlorin loss was made up for by a subsequent decreased excretion, which caused an abnormal retention.

TABLE 3.—METABOLISM STUDIES OF WATER—

Name	Period	Water Balance, C.c.							Chlorin Bal., Gm.	
		Intake by Mouth	Injected	Total Intake	Urine	Feces	Total Excretion	Retained	Intake by Mouth	Injected
1. I. G.	Before injection (daily aver,)	725	.....	725	273	115	388	337	0.5467	.....
	1st day after....	805	210	1,015	285	205	490	525	0.6070	1.160
	2d day after....	825	.....	825	450	101	551	274	0.6221	.....
2. E. K.	Before injection (daily aver,)	603	.....	603	383	15	398	205	0.3260	.....
	1st day after....	710	210	920	570	25	595	325	0.3840	1.1598
	2d day after....	730	.....	730	390	65	455	275	0.3950	.....
	3d day after....	785	.....	785	450	47	497	288	0.4240	.....
3. J. C.	Before injection (daily aver,)	553	.....	553	113	195	308	245	0.3526	.....
	1st day after....	595	220	815	163	216	379	436	0.2654	1.650
	2d day after....	679	.....	679	140	234	374	305	0.4805	.....
	3d day after....	553	.....	553	160	220	380	173	0.4002	.....
4. T. M.	Before injection (daily aver,)	828	.....	828	278	303	581	247	0.5887	.....
	1st day after....	1,067	208	1,275	830	199	1,029	246	2.5909	0.520
	2d day after.... (2d injection)	660	160	820	450	98	548	272	0.2194	1.200
	3d day after.... (13½ hr. only)	540	.....	540	335	85	420	120	0.1659	.....
5. V. V.	Before injection (daily aver,)	623	.....	623	393	31	424	199	0.3670	.....
	1st day after....	620	210	830	320	85	405	425	0.3654	1.160
	2d day after....	625	.....	625	360	26	386	239	0.3684	.....
	3d day after....	630	.....	630	260	27	287	343	0.3713	.....
6. J. B.	Before injection	985	.....	985	393	262	655	330	0.8570	.....
	1st day after....	885	205	1,090	450	200	650	440	0.7837	1.025
	2d day after....	1,095	.....	1,095	450	176	626	469	0.8953	.....
	3d day after....	1,010	.....	1,010	600	257	857	153	0.6319	.....
7. L. M.	Before injection	550	.....	550	93	133	226	324	0.4175	.....
	1st day after....	535	180	715	105	166	271	444	0.4061	0.9936
	2d day after.... (attempt at 2d inj.)	530	30	560	100	202	302	258	0.4023	0.1218
	3d day after....	550	.....	550	190	101	291	259	0.4175	.....
	4th day after....	545	.....	545	180	45	225	320	0.4137	.....
8. J. P.	Before injection	384	.....	384	54	240	294	90	0.2565	.....
	1st day after....	440	200	640	40	85	125	515	0.2536	0.8480
	2d day after.... (2d injection)	485	220	705	205	472	677	28	0.4560	1.2950
	3d day after.... (3d injection)	450	220	670	200	274	474	196	0.4230	1.100
	4th day after.... (4th injection)	570	225	795	250	411	661	134	0.5370	0.960
	5th day after....	165	.....	165	95	396	491	—326	0.1550	.....
	6th day after....	185	.....	185	65	230	295	—110	0.1740	.....
9. C. B.	Before injection (daily aver.)	543	.....	543	283	94	377	166	0.6142	.....
	1st day after....	595	205	800	355	166	521	279	0.6757	1.1316
	2d day after.... (2d injection)	545	225	770	270	200	470	300	0.5757	1.1070
	3d day after....	620	.....	620	360	133	493	127	0.3334	.....
	4th day after.... (3d injection)	530	220	750	275	124	399	351	0.2768	1.2540
	5th day after....	610	.....	610	395	91	486	124	0.3274	.....
	6th day after....	645	.....	645	345	148	493	152	0.3418	.....

Chlorin Balance, Gm.					Summary
Total Intake	Urine	Feces	Total Excretion	Retained	
0.5467	0.1840	0.1410	0.3250	0.2217	Less than half the water and chlorin injected eliminated in 48 hours; the water excreted in the urine, the chlorin in both urine and first day's feces
1.7670	0.4480	0.2118	0.6598	1.1072	
0.6221	0.5240	0.1044	0.6284	—0.0063	
0.3260	0.3734	0.0080	0.3814	—0.0554	Part of the injected water eliminated the first day, mainly in the urine; on the two following days excretion so reduced in relation to intake by mouth that more than the amount injected was retained; no injected chlorin eliminated during the period of observation
1.5438	0.4390	0.0195	0.4585	1.0853	
0.3950	0.2690	0.0512	0.3202	0.0748	
0.4240	0.4050	0.0374	0.4424	—0.0184	
0.3526	0.0093	0.5539	0.5632	—0.2106	A small part of both water and chlorin injected was eliminated, mainly through the feces, in the three days of observation; the urine excretion was very low throughout the period
1.9154	0.0360	0.6212	0.6572	1.2582	
0.4805	0.0180	0.7268	0.7448	—0.2643	
0.4002	0.0120	0.6720	0.6840	—0.2838	
0.5887	0.3660	0.0482	0.4142	0.1745	The injected water was mostly eliminated through the urine the first and second days, the water in the feces being greatly reduced; no injected chlorin eliminated; the somewhat increased chlorin excretion in both urine and feces removed only part of the large chlorin intake by mouth of the first day, due to a mistake in adding salt to the barley water
3.1109	0.5271	0.1089	0.6360	2.4749	
1.4194	0.6075	0.0889	0.6964	0.7230	
0.1659	0.1977	0.0933	0.2910	—0.1251	
0.3670	0.3062	0.0171	0.3233	0.0437	No injected water eliminated in the period of observation; all the injected chlorin excreted, mainly through the urine of the first and second days
1.5254	1.040	0.0763	1.1163	0.4091	
0.3684	0.6320	0.0230	0.6550	—0.2866	
0.3713	0.3960	0.0245	0.4205	—0.0492	
0.8570	0.2223	0.3788	0.6011	0.2559	Not all the injected water eliminated in the three days of observation; the increased excretion in the urine; practically all the injected chlorin eliminated in the urine of the first day and in the feces of the third day
1.8087	0.8235	0.3291	1.1526	0.6561	
0.8953	0.1260	0.3653	0.4913	0.4040	
0.6319	0.1080	0.7580	0.8660	—0.2341	
0.4175	0	0.2016	0.2016	0.2159	All the injected water eliminated, partly in the feces of the first and second days, and partly in the urine of the third and fourth days; about half the injected chlorin eliminated through the feces of the first and second days; no excretion of chlorin in the urine during the period of observation
1.3097	0	0.4878	0.4878	0.9119	
0.5241	0	0.5934	0.5934	—0.0693	
0.4175	0	0.2161	0.2161	0.2014	
0.4137	0	0.0951	0.0951	0.3186	
0.2565	0.0912	0.1141	0.2053	0.0512	All the water of the four successive injections eliminated through the urine and feces, beginning the second day; increased excretion was continuing on the sixth day; nearly all the injected chlorin eliminated through both urine and feces, the increased excretion beginning on the second day; with decreased intake by mouth, excretion through the urine decreased, returning to normal on the sixth day; that through the feces was still high on the fifth and sixth days
1.1016	0.0960	0.0474	0.1434	0.9582	
1.7510	0.7200	0.2646	0.9846	0.7664	
1.5230	0.8960	0.4750	1.3710	0.1520	
1.4970	0.8800	0.7110	1.5910	—0.0940	
0.1550	0.3440	0.6840	1.0280	—0.8730	
0.1740	0.0800	0.3970	0.4770	—0.3030	
0.6142	0.3840	0.1409	0.5249	0.0893	Less than half the injected water eliminated during the period of observation, practically all the increased excretion being in the feces, which were still greater than normal on the sixth day; the larger part of the injected chlorin was eliminated during the period of observation by a small daily increase in both urine and feces; excretion was nearly normal in the urine, slightly increased in the feces on the sixth day
1.8073	0.5920	0.3440	0.9360	0.8713	
1.6827	0.6000	0.4160	1.0160	0.6667	
0.3334	0.5920	0.2170	0.8000	—0.4756	
1.5308	0.5280	0.2020	0.7300	0.8008	
0.3274	0.5796	0.1470	0.7266	—0.3992	
0.3418	0.3400	0.2400	0.5800	—0.2382	

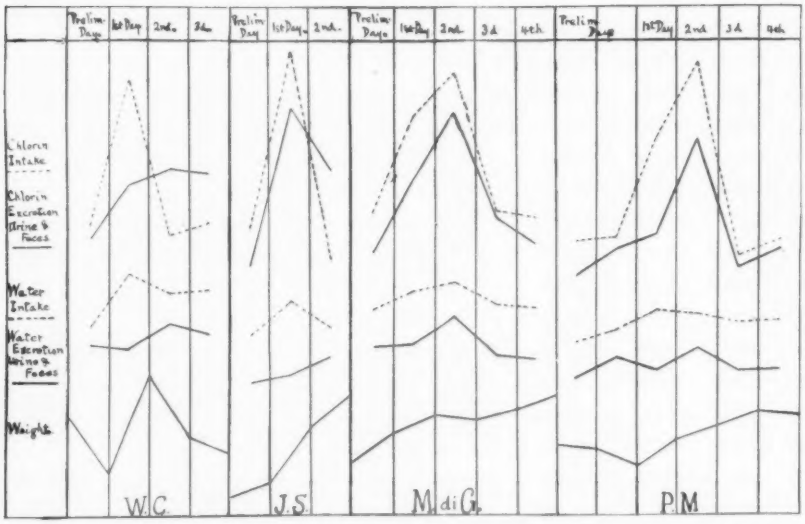

Fig. 1.—Chlorin and water intake and excretion in four normal children.

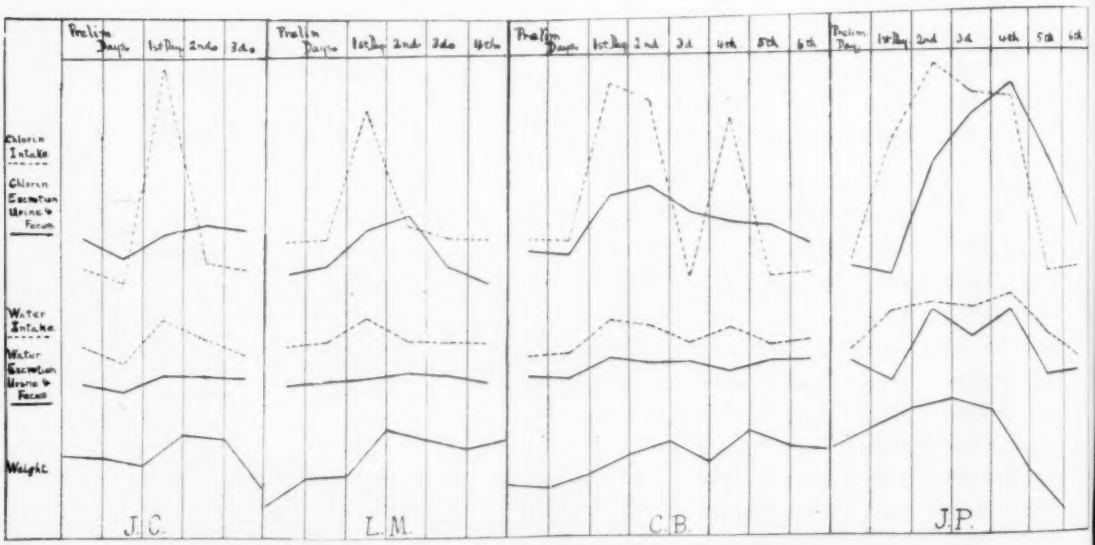

Fig. 2.—Chlorin and water intake and excretion in four abnormal children.

Among the nine abnormal children, only three lost all the injected water during the time of observation—one in the first day, one in four days and one in six days; four excreted part of the water in the period of observation—two, three or six days; two lost little or none in three days. Of the injected chlorin, one infant eliminated all in two days, one in three and one in six days; three excreted only part in the period of observation — two, four or six days; three lost practically none in the three days of observation. No excessive loss beyond the amount injected of either water or chlorin took place with any of the abnormal children. In one case there was an abnormal retention of water after the elimination of part of that injected.

TABLE 4.—EXCRETION OF WATER INJECTED IN THE CASE OF TWENTY-FOUR CHILDREN

	Normal	Abnormal
All excreted in one day	6	1
Not entirely excreted in period of observation	8	6
Practically none excreted in period of observation	3	2

TABLE 5.—EXCRETION OF CHLORIN INJECTED IN THE CASE OF TWENTY-FOUR CHILDREN

	Normal	Abnormal
All excreted in one day	6	0
Not entirely secreted in period of observation	5	6
Practically none excreted in period of observation	0	3

The loss of the water injected in the normal children took place in ten cases through the urine, in one mainly through the feces, and in one through both. The chlorin in fourteen cases was excreted through the urine; in one equally in the urine and feces. In one of the normal children, in whom diarrhea had developed shortly before the injection, excretion of the injected water took place wholly, and the chlorin partly, through the feces. The injected water and chlorin with the abnormal children was excreted mainly through the urine in two cases, through the feces in two, and about equally through both in three cases. With the children in whom elimination took place through the feces, diarrhea was always present before hypodermoclysis. In one normal child, to whom an unintentionally large amount of salt had been given, diarrhea developed on the second day, the injected water having already been eliminated in the urine.

The cases in which several injections were made on successive days

merit special consideration. Two patients (C. B. and J. P., Table 3) received, respectively, three and four injections in four days. Both were suffering from diarrhea and both were very ill. The one with the most severe diarrhea (J. P.) excreted slightly more water than the amount injected, and nearly all the chlorin. The other (C. B.) retained a significant amount of both water and chlorin during the period of observation.

TABLE 6.—SODIUM CHLORID EXCRETION IN—

Period	R. S., Day Beginning 12 M.				H. R., Day Beginning 10 A. M.				J. M., Day Beginning 10:30 A. M.			
	Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.	
	Intake*	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine
1st day												
1	.....	262	.....	0.9777	.....	135	.....	0.2295	.....	160	.....	0.7867
2	.....	80	.....	0.0992	.....	210	.....	0.2940	.....	90	.....	0.7812
3	.....	125	.....	0.4113	.....	165	.....	0.2360	.....	90	.....	0.6660
4	.....	110	.....	0.2695	.....	190	.....	0.2337	.....	70	.....	0.4928
Total..	1,311	577	2.3094	1.7577	1,343	700	1.9064	0.9932	630	410	3.7770	2.7267
2d day												
1	.....	.....	.....	.....	.....	300	.....	0.4230	.....	100	.....	0.7080
2	.....	.....	.....	.....	.....	155	.....	0.2408	.....	80	.....	0.5920
3	.....	.....	.....	.....	.....	155	.....	0.2356	.....	110	.....	0.1342
4	.....	.....	.....	.....	.....	185	.....	0.1933	.....	95	.....	0.4104
Total..	.....	.....	.....	.....	1,121	795	0.7262	1.0922	521	385	1.0802	1.8446
3d day												
1	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....
2	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....
3	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....
4	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....
Total..	.....	.....	.....	.....	.....	.....	.....	.....	.....	...	.....	.....

* The figures for the intake of water include the amount taken by injection.

The inference from these two cases seems warranted that repeated injections may be made without harm, and in some patients the water and salt is retained long enough to be of positive benefit. The increase in the diarrhea noted in the case of J. C. could hardly, under the conditions existing, be attributed to the injection. The beneficial effects of repeated injections in diarrheal cases have been abundantly confirmed by clinical observations.

Since in some cases the injected salt was entirely eliminated in the first twenty-four hours, it seemed desirable to collect the urine in shorter periods, in order to see how soon the increased excretion began. With six children, therefore, the collection of urine following hypodermoclysis was made in six-hour periods. The results are shown in Table 6.

A study of the water and chlorin excretion in this series showed

—Six-Hour Periods Following Hypodermoclysis

J. S., Day Beginning 9:15 A. M.				W. C., Day Beginning 11:30 A. M.				P. D., Day Beginning 10 A. M.			
Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.		Water, C.c.		Chlorin, Gm.	
Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine	Intake	Urine
.....	40	.....	0.1920	.....	140	.....	0.1456	.....	65	.....	0.1277
.....	70	.....	0.6328	.....	195	.....	0.2496	.....	170	.....	0.3689
.....	75	.....	0.6705	.....	155	.....	0.2232	.....	210	.....	0.3276
.....	35	.....	0.2842	.....	210	.....	0.2352	.....	130	.....	0.2197
884	220	2.3603	1.7795	1,280	700	1.6890	0.8536	1,245	575	1.8805	1.0439
.....	20	.....	0.1264	.....	240	.....	0.1440	.....	190	.....	0.1824
.....	225	.....	0.8460	.....	205	.....	0.1968	.....	80	.....	0.0984
.....	60	.....	0.3096	.....	155	.....	0.3038	.....	235	.....	0.3596
.....	25	.....	0.1280	.....	230	.....	0.3036	.....	165	.....	0.2541
695	330	0.7807	1.4100	1,125	830	0.4716	0.9482	1,006	670	0.6940	0.8945
.....	130	.....	0.6578	.....	190	.....	0.1976	.....	205	.....	0.1825
.....	70	.....	0.3178	.....	190	.....	0.1444	.....	40	.....	0.0352
.....	...	.....	.....	.....	180	.....	0.2952	.....	210	.....	0.1701
.....	...	.....	.....	.....	230	.....	0.3036	.....	220	.....	0.2024
.....	...	.....	.....	1,130	790	0.5744	0.9408	1,065	675	0.7160	0.5902

a striking want of uniformity. This was true not only of the different children, but of the same child on different days. One child (R. S.) eliminated a very large part of his chlorin intake in the first six hours; very little in the second six hours; and again, quite large amounts in the third and fourth periods. H. R. and J. H. excreted almost uniform amounts in all the periods of the two days. The other three children were alike in eliminating little or none of the injected chlorin in the

first period, but differed greatly in the distribution of the excretion after that.

Again, there was no uniform relation of water excretion to that of chlorin. Although the excretion of the two frequently ran parallel, there were many instances in which the opposite was true. Among the individual factors influencing the manner of excretion of the hypodermoclysis solution, the rate of absorption is probably a very important one.

CONCLUSIONS

1. In acute diarrhea much salt and water are lost from the body. A similar condition is seen in marasmus, and after protracted vomiting, etc. When saline solutions are injected in such subjects a considerable amount of the salt is usually held for two or three days, and occasionally for a longer period.

2. If in these infants the variations in the loss of water by the skin and lungs can be ignored, the retention of water usually follows closely that of the salt.

3. Our metabolism studies support the clinical conclusions as to the beneficial effects of repeated saline injections in the conditions mentioned.

4. With normal children and with convalescents without evidence of dehydration, great variation is observed in the excretion of the injected water. It may be excreted very rapidly in the course of the first twenty-four hours, or part or all of it may be held for several days. The salt, however, is usually excreted rapidly, sometimes a large part of it in the first six hours.

THE FACTOR OF INANITION IN THE DEVELOPMENT OF ACETONURIA IN CHILDREN*

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Until very recently the terms acidosis and acetonuria have been used more or less as synonyms, but at the present time there is a tendency to use the term acidosis in a more general way and in a stricter chemical sense, as designating a condition in which there is a decreased alkaline reserve in the blood as a result of an overproduction or decreased elimination of acid bodies. We are interested in this paper only in that specific form or phase of acidosis which is distinguished from the others by the excessive formation of acetone, diacetic acid and beta-hydroxybutyric acid, or the so-called acetone bodies. It is a specific form of acidosis, in that faulty metabolism of the fats takes place, leading to the formation of these definite substances, while the other forms of acidosis are the result in many instances of very unclear processes.

Without entering on a detailed historical résumé we can briefly state the present condition of our knowledge in regard to these substances. For many years it has been known that acetone appeared in the urine of fasting individuals, after narcosis, in certain febrile and toxic conditions, and above all, in diabetes. Later it was shown that beta-hydroxybutyric acid was eliminated with the acetone and that it had the same origin, and further, that the extent of the acidosis could not be estimated from the acetone alone. However, it has only been in the last few years, as a result of the introduction of Shaffer's method, that the quantitative estimation of beta-hydroxybutyric acid has been satisfactory and feasible. For some time it has been a quite generally accepted view that the formation of the acetone bodies from the failure of proper metabolism of the fats is secondary to an insufficient utilization of carbohydrate. Magnus-Levy[1] makes the following statement:

> Formerly, numerous varieties of acetonuria were distinguished, such as those occurring in inanition, in fever, in infection and intoxication, in diseases of the stomach and intestine, in nervous and mental affections, etc. All the above-named forms of acetonuria can, however, be referred to the same and

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* Read before the Section on Diseases of Children at the Sixty-Seventh Annual Session of the American Medical Association, Detroit, June, 1916.

* From the Department of Pediatrics, Washington University Medical School, and the St. Louis Children's Journal.

1. Magnus-Levy: v. Noorden's Metabolism and Practical Medicine, London, 1907, **1**, 171.

identical cause, just as the acidosis of diabetes can, namely, the entire, or almost entire, deficiency of carbohydrates in the metabolism.

This summarizes very well what might be considered the generally accepted viewpoint.

As a result of the recent work of Allen[2] and other American workers in diabetes, however, there seems to be reason to question the correctness of this view. It has been shown that a diabetic acetonuria may be lessened by fasting and this has occurred in some cases when the dextrose-nitrogen ratio was approximately 3.6 to 1, or at a time when the body was almost entirely unable to oxidize sugar. Moreover, other chemists, as Taylor, hold a different view. Taylor[3] holds that certain clinical and experimental facts, as well as theoretical considerations, are opposed to this view of carbohydrate deficiency. For example, he considers the severe acidosis seen at times following narcosis as "not one associated with the carbohydrate metabolism; it is a result of the necrosis of the liver." Likewise, in other conditions, as cyclic vomiting, in which acetonuria occurs, Taylor does not believe that carbohydrate insufficiency is the cause of the acidosis.

The subject is of particular interest to the pediatrician, as despite the infrequency of diabetes at this age period, acetonuria is very common in childhood and its association with narcosis, cyclic vomiting, and many febrile and toxic conditions is often seen. In all of these clinical conditions there is the possibility that inanition may be a factor to a greater or less degree. But the actual rôle played by inanition is very uncertain, for, as stated above, persistent fasting in some cases of diabetes seems to decrease the degree of acidosis. We have been surprised at the paucity of actual studies of ketonuria and fasting. Our knowledge is practically all derived from observations on professional fasters, and although the earlier writers, as Brugsch, give figures, in the last study of this kind, that by Benedict[4] on the faster Levanzin in Boston in 1912, the chemical methods used were so defective that in a discussion of the acidosis the only conclusion reached was that "there was a material excretion of beta-oxybutyric acid."

As a part of a general study of acetone body acidosis in childhood, it has seemed essential to obtain figures of the degree of acetonuria resulting from inanition. So far as we know no figures exist on this point. Not only is this essential before acetonuria accompanying pathologic conditions can be studied, but inanition is so frequently used as a therapeutic measure in childhood that it is of interest to know how children react to the method of treatment.

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2. Allen, F. M.: Jour. Am. Med. Assn., 1916, **66,** 1525.
3. Taylor, A. E.: Digestion and Metabolism, Philadelphia, 1912, p. 358.
4. Benedict: A Study of Prolonged Fasting, Publication of Carnegie Institute No. 203, 1915.

The method used for examination of the urine was that of Shaffer[5] in which the acetone and diacetic acid are distilled and determined by the iodimetric method of Messinger, and the beta-hydroxybutyric acid oxidized by potassium bichromate to acetone and determined in terms of the latter. Not all the acetone formed is excreted in the urine, but some uncertain and indefinite amount is eliminated through the lungs. To just what extent such elimination takes place is hard to determine. Some of the older papers give the impression that a large part may be eliminated in this way, but in a more recent study Folin and Denis[6] found that "the total acetone excretion with the breath in starvation is quantitatively insignificant." The method of calculating the expired acetone by analyzing small portions contains so many pitfalls, we decided the error would be less if this were left out of consideration and the amount of acetonuria used to express the degree of acidosis. The children used were on a standard metabolic diet previous to the experiments, in which from 40 to 50 per cent. of the total calories were in the form of carbohydrate. The general plan was to obtain a normal twenty-four hour excretion on this diet and then make determinations on twenty-four hour periods of inanition. The period of inanition varied in length as indicated below. At the close of the inanition the child was placed on the previous diet and twenty-four hour specimens were examined until a return to normal figures occurred.

The total quantity of acetone bodies in the urine during short inanition periods varies directly with the duration of the inanition. In five instances food was given at the end of twenty-four hours, and in the remainder the inanition period lasted forty-eight hours. The figures for the total quantity differed very widely, and hence we can best compare the results by expressing the degree of acetonuria in terms of kilograms of body weight. As might be expected, the total output in an infant is much less than in a child of 10 years. When on a complete diet the average amount of acetone bodies eliminated was about 0.003 gm. per kilogram of body weight (extremes from 0.001 to 0.007). In eight of eighteen cases studied the amount excreted in the first twenty-four hours was within these limits and averaged about 0.004 gm. In the remainder there was an increase, averaging about ten times the normal, or 0.030 gm. per kilogram. As a whole we can say that there is but little increased output of acetone bodies during a period of twenty-four hours inanition in a healthy child. In the cases (Cases 1, 2, 3, 6 and 12) in which inanition was terminated at the end of twenty-four hours, there was a continued increased elimination of acetone on the following day, which in some instances was greater than

5. Shaffer: Jour. Biol. Chem., 1913, **16,** 265.
6. Folin and Denis: Jour. Biol. Chem., 1915, **21,** 183.

EFFECT OF INANITION ON ACETONURIA IN CHILDREN

Case No.	Condition as to Diet	Acetone and Diacetic Acid	Beta-hydroxy-butyric Acid	Total Acetone	Total Acetone per Kilo Body Wt.	Total Nitrogen	Ammonia Nitrogen	Per Cent. Ammonia Nitrogen	Remarks
1	Normal day	0.007	0.015	0.022	0.0037	1.789	0.173	10	Weight, 5.9 kg.; age, 3 mo. Fairly well nourished
	1st inanition	0.017	0.019	0.036	0.006	1.037	0.11	10.5	
	Return	0.029	0.042	0.071	0.012	1.712	0.198	11.5	
2	Normal day	0.01	0.007	0.017	0.0028	1.869	.....	....	Weight, 6.05 kg.; age, 8 mo. Good nutrition, but underweight
	1st inanition	0.086	0.157	0.243	0.04	1.709	0.365	21	
	Return	0.02	0.016	0.036	0.006	1.682	0.31	18	
3	Normal day	0.02	0.02	0.04	0.006	2.155	0.3	14	Weight, 6.48 kg.; age, 8 mo. Thin
	1st inanition	0.029	0.044	0.073	0.011	1.037	0.118	11	
	Return	0.039	0.025	0.054	0.01	1.154	0.141	12	
4	Normal day	0.01	0.014	0.024	0.002	1.667	0.125	7.5	Weight, 10.7 kg.; age, 10 mo. Well nourished; fat
	1st inanition	0.016	0.032	0.048	0.005	1.845	0.133	7.2	
	2d inanition	0.07	0.179	0.249	0.024	1.831	0.502	27	
	Return	0.04	0.088	0.128	0.012	1.93	0.487	25	
5	Normal day	0.037	0.012	0.049	0.004	2.525	0.245	9.8	Weight, 11.2 kg.; age, 18 mo. Fat; overnourished
	1st inanition	0.11	0.111	0.221	0.02	2.463	0.253	10.2	
	2d inanition	0.505	3.914	4.419	0.416	3.54	0.54	15	

	2d inanition	0.505	3.914	4.419	0.416	3.54	0.54	15	
6	Normal day	0.009	0.013	0.022	0.002	3.224	0.154	4.8	Weight, 12 kg.; age, 2 years. Well nourished
	1st inanition	0.052	0.128	0.18	0.015	2.777	0.143	5.2	
	2d inanition	0.126	0.474	0.599	0.05	4.348	0.4	9	
	Return	0.017	0.019	0.036	0.003	2.578	0.167	6.5	
7	Normal day	0.013	0.025	0.038	0.004	4.762	0.301	6.3	Weight, 8.7 kg.; age, 2 years. Poorly nourished; underweight
	1st inanition	0.15	0.447	0.627	0.072	3.295	0.191	5.8	
	2d inanition	0.315	1.041	1.356	0.159	3.462	0.562	16	
	Return	0.087	0.235	0.322	0.039	3.344	0.713	21.5	
	Normal	0.021	0.022	0.043	0.005	4.608	0.953	20.5	
	Normal	0.012	0.026	0.038	0.005	5	0.465	9.3	
8	Normal day	0.031	0.04	0.071	0.005	4.624	0.202	4.3	Weight, 13.5 kg.; age, 2 years. Fat; overnourished
	1st inanition	0.037	0.07	0.107	0.008	1.672	0.114	6.8	
	2d inanition	0.429	2.167	2.596	0.2	2.958	0.377	12.7	
9	Normal day	0.025	0.037	0.062	0.003	6.493	0.16	2.5	Weight, 24 kg.; age, 7 years. Somewhat undernourished.
	1st inanition	0.1	0.156	0.256	0.011	6.25	0.18	3	
	2d inanition	0.45	1.235	1.685	0.07	7.407	0.45	6	
	Return	0.132	0.373	0.505	0.021	10.929	0.578	5.2	
	Normal	0.011	0.023	0.034	0.001	6.896	0.338	5	
	Normal	0.018	0.031	0.049	0.002	7.038	0.302	5	

EFFECT OF INANITION ON ACETONURIA IN CHILDREN

Case No.	Condition as to Diet	Acetone and Diacetic Acid	Beta-hydroxy-butyric Acid	Total Acetone	Total Acetone per Kilo Body Wt.	Total Nitrogen	Ammonia Nitrogen	Per Cent. Ammonia Nitro-gen	Remarks
10	Normal day.....	0.012	0.045	0.057	0.003	8.205	0.356	4.3	Weight, 21 kg.; age, 7 years. Thin; undernourished
	1st inanition.....	0.375	2.37	2.745	0.131	7.3	0.33	4.5	
	2d inanition.....	0.765	3.044	3.809	0.18	7.425	0.785	10.5	
	Return.....	0.348	1.129	1.477	0.072	10.87	1.195	11	
11-1	Normal day.....	0.01	0.075	0.085	0.002	9.259	0.497	5.3	Weight, 34.5 kg.; age, 11 years. Very well nourished
	1st inanition.....	0.405	1.2	1.605	0.046	7.518	0.329	4.5	
	2d inanition.....	0.846	2.745	3.591	0.104	7.143	0.792	11	
	Return.....	0.43	1.123	1.553	0.045	9.07	1.117	12.5	
11-2	Normal day.....	0.013	0.029	0.042	0.001	7.055	0.194	2.7	Weight, 34.5 kg.; age, 11 years. Same as Case 11.
	1st inanition.....	0.037	0.041	0.078	0.002	5.917	0.152	2.5	
	2d inanition.....	0.92	3.435	4.355	0.127	8.18	0.41	5	
	Return.....	0.36	1.108	1.468	0.043	10.596	1.132	10.5	
12	Normal day.....	0.03	0.07	0.1	0.004	13.745	0.438	3.2	Weight, 26.3 kg.; age, 11 years. Very thin and undernourished
	1st inanition.....	0.112	0.324	0.436	0.016	7.752	0.327	4.2	
	2d inanition.....	0.12	0.429	0.549	0.028	13.072	0.568	4.3	
13	Normal day.....	0.015	0.113	0.128	0.004	10.526	0.404	3.8	Weight, 35.4 kg.; age, 10 years. Fat; overnourished
	1st inanition.....	0.05	0.065	0.115	0.003	6.944	0.232	3.3	
	2d inanition.....	0.315	0.705	1.02	0.029	9.231	0.465	5	
	Return.....	0.09	0.259	0.349	0.01	13.468	0.695	5	

14	Normal day	0.025	0.027	0.052	0.002	8.772	0.305	3.5	Weight, 24 kg.; age, 11 years. Thin; undernourished
	1st inanition	0.055	0.099	0.154	0.006	6.896	0.206	3	
	2d inanition	0.12	0.334	0.454	0.019	4.878	0.197	4	
15	Normal day	0.015	0.30	0.045	0.002	10.695	0.375	3.5	Weight, 25.4 kg.; age, 10 years. Thin; undernourished
	1st inanition	0.5	1.441	1.941	0.078	5.312	0.332	6.2	
	2d inanition	1.26	4.93	6.19	0.254	8.13	1.143	14	
	Return	0.5	1.094	1.594	0.066	11.204	1.242	11.1	
16	Normal day	0.008	0.004	0.012	0.003	0.568	0.168	29	Weight, 3.5 kg.; age, 3 mo. Fairly well nourished
	1st inanition	0.007	0.006	0.013	0.003	0.4	0.105	26	
	2d inanition	0.033	0.021	0.054	0.015	0.653	0.12	18	
	Return	0.016	0.013	0.029	0.008	0.615	0.082	13	
	Normal	0.008	0.009	0.017	0.005	0.358	0.075	20	
17	Normal day	0.01	0.013	0.023	0.003	3.96	0.158	4	Weight, 9.2 kg.; age, 17 mo. Fairly well nourished
	1st inanition	0.016	0.013	0.029	0.003	2.273			
	2d inanition	0.042	0.035	0.077	0.009	2.777	0.394	14.2	
	3d inanition	0.017	0.023	0.04	0.005	1.101	0.122	11	
	Return	0.037	0.038	0.075	0.009	3.472			
	Normal	0.023	0.032	0.055	0.006	2.747			
18	1st inanition	0.4	1.464	1.864	0.2	2.174	0.383	17	Weight, 9.3 kg.; age, 18 mo. Thin; undernourished. Post-operative
	2d inanition	0.925	3.312	4.237	0.455	4.255	0.99	23	

the amount eliminated on the day of the inanition. This fell rapidly, so that by the second day normal figures were again obtained.

In the remaining cases the inanition period was continued for a second twenty-four hours before the child was placed on the original diet. A rapid increase in acetone elimination took place during the second twenty-four hours. The most marked increase occurred in a well-nourished baby of 18 months (Case 5), in whom the acetone and diacetic acid jumped from 0.110 to 0.505 gm. and the beta-hydroxybutyric acid from 0.416 to 3.914 gm., or an increase from 0.02 to 0.416 gm. per kilogram of body weight. The greatest absolute amounts excreted were by a boy of 10 years (Case 15), who eliminated 1.26 gm. of acetone and 4.93 of beta-hydroxybutyric acid on the second day. The average amount excreted on the second day was about 0.15 gm. per kilogram of body weight.

On the day following two inanition days there was a continued acetonuria, but this was always less than the amount excreted on the second day of the inanition, contrary to what was at times found following one inanition day. On the second day following normal figures were obtained.

We have as yet very few data regarding pathologic conditions associated with acetonuria with which to compare these figures. Dr. Jeans is studying the acidosis of narcosis and we are investigating febrile and toxic conditions. The postoperative studies so far made do not show figures higher than these, and the figures from patients with pneumonia at its height and other febrile conditions are lower. In two cases of diabetes studied in our clinic which had a slight acidosis on diet, there was a decrease on a fasting day and an increase on the day following the fast, when a small amount of food was given. The figures did not exceed those obtained in these studies for inanition in healthy children.

In the discussion of the total acetonuria we have not considered the nutrition of the individual. There has been a rather widespread idea that the fat individual excretes more acetone bodies than the thin. This is perhaps the result of a paper by Brugsch[7] in 1905, in which he reported that a professional faster, who was in a fair condition of nutrition at the end of a prolonged fast, eliminated acetone bodies in the urine, while none were present in the urine of a patient with a stenosing carcinoma of the esophagus, who was so emaciated from starvation that there then was no longer any body fat present. Folin and Denis[6] have recently published the results of short fasts in two obese women and reached the conclusion that obesity is not a predisposing or contributing factor in the onset or intensity of the acidosis of starvation. As some of our children of the same age were fat and overnourished, and others thin and undernourished, they furnish some

7. Brugsch: Ztschr. f. exper. Path. u. Therap., 1905, **1**, 419.

further confirmation of Folin and Denis' conclusion. For this comparison the total amount of acetone bodies for the two inanition days and the day following are added together. In Case 15, a poorly nourished lad of 11 years weighing 25 kg. excreted 9.725 gm., and an overnourished obese boy of 11 (Case 13), weighing 35 kg. excreted only 1.484 gm. in the three days. Another overnourished boy of 11, weighing 34 kg. (Case 11) excreted at one period 6.749 and at another 5.901 gm., or less than the undernourished boy. In some infants this same condition held; that is, there was no relation between the degree of acetonuria and the state of the child's nutrition. The children between whom these comparisons were made had all been on the same fixed diet before the period of inanition.

As was the observation with previous observers, we found that the amount of beta-hydroxybutyric acid (in terms of acetone) eliminated was as a rule from two to four times as much as the quantity of combined acetone and diacetic acid.

The nitrogen and ammonia of the urine was determined daily. There was at most a very slight actual increase or percentage increase in the ammonia elimination on the first day of inanition, and this in but a few cases. On the second day of inanition, however, a marked increased took place.

All of the children were closely watched for the development of clinical symptoms, particularly those which are so frequently regarded as signs of an acetone body acidosis in childhood. Not one child showed nausea, vomiting, flushing of the cheeks, temperature or hyperpnea. Except for some hunger in a few cases, not a child seemed to be affected in any way by the inanition. It seems hard to believe from our studies that the formation of acetone bodies per se, at least in the amounts produced by inanition, can be the fundamental cause of the symptoms so often regarded as due to acidosis.

The table contains the data for the different children studied.

INFANTILE SCURVY

IV. THE THERAPEUTIC VALUE OF YEAST AND OF WHEAT EMBRYO*

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Although we possess in orange juice a specific for infantile scurvy, it is well worth while to look about for other therapeutic agents which are potent in this disturbance. This is desirable from several points of view. In the first place, orange juice cannot be considered an ideal antiscorbutic food, as it is expensive and under certain circumstances difficult to procure, but more especially because it cannot well be embodied in the food. As a result of its having to be prepared and given separately, it is frequently forgotten by the physician or by the nurse, with the result that we encounter cases of latent or subacute scurvy which have come about through this oversight. Furthermore, as long as the true nature of the antiscorbutic vitamin is unknown, we shall gain valuable knowledge of the essential chemical substance which forms the basis of this disorder by ascertaining substances that do or do not possess antiscorbutic power. It was with these objects in view that yeast was resorted to in the prevention and cure of certain cases which have been reported in other connections. As is well known, yeast has been found to act as a specific in the prophylaxis and cure of beriberi, a disease which develops generally as the result of a diet of polished rice. In a previous paper[1] dealing with scurvy the intimate clinical relationship between these two deficiency diseases was pointed out, it being shown that in both there is involvement of the heart as well as of the central nervous system. Further observations have served only to strengthen our conviction of the group relationship between these two nutritional disorders. We hope to discuss in greater detail this clinical similarity at another time; however, it is evident that we might well expect that yeast would also prove of value in infantile scurvy. The diets of the infants on whom we wish to report consisted of preparations of pasteurized milk, with the addition of cereal in the case of those over 6 months of age. The milk was of excellent quality and had been pasteurized at 145 F. for thirty minutes. The only change which was made in the diet was the omission of orange juice, and the substitution of yeast in its stead, or in the case of very young

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* Read in abstract before the Society of Experimental Biology and Medicine, May 24, 1916, Proceedings, **13,** 145.

1. Hess, A. F.: Jour. Am. Med. Assn., 1915, **65,** 1003.

infants who had not yet received orange juice, yeast was introduced into the dietary. The yeast was a fluid preparation, which was autolyzed and was prepared as follows: As soon as it was obtained from the brewery it was pressed to a consistency of putty, and was then allowed to autolyze in a thermostat for forty-eight hours. This fluid was of syrupy consistency, and as it contained considerable solid matter, composed mainly of the walls of the erupted yeast cells, it was diluted somewhat and filtered. It finally had a specific gravity of about 1.04. One or two tablespoonfuls of this fluid was added directly to the day's feeding of milk, or, in case the milk was not well taken, was given with a spoon.

The instances in which the yeast was given instead of orange juice to infants 6 months of age or under, in order to prevent the occurrence of scorbutic symptoms, are naturally the most interesting and signifi-

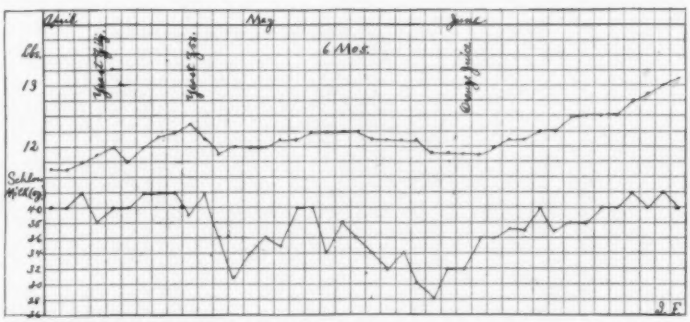

Chart 1.—Failure of yeast as a prophylactic; subacute scurvy promptly yielding to orange juice.

cant, for it is evident that if it failed as a prophylactic, it could hardly prove to possess curative powers. We may summarize our experiences in this regard by the statement that our hopes of the efficacy of this therapeutic agent proved to be unfounded, as the young infants developed some signs of subacute or latent scurvy in spite of receiving the autolyzed yeast. The symptoms were not marked, and were promptly counteracted by the administration of orange juice; however, they were sufficiently definite to enable one to make a reliable diagnosis. The weight charts of two of these cases are appended (Charts 1 and 2), but must be regarded as unsatisfactory, as failure to gain in weight is but one sign of incipient scurvy, in some cases by no means the most significant one; in others, as pointed out elsewhere, it was entirely lacking. It will therefore be well to add a few details regarding these cases. The case portrayed in Chart 1 was that of a fairly well-nourished infant who had gained steadily until it was 5 months of age,

when it weighed about 11¼ pounds. It had been on Schloss milk[2] and had gained 3 pounds in the preceding two months. As it had hardly gained anything in the three weeks just elapsed, yeast was given in the beginning of April, as the chart indicated. In spite of the fact that yeast was continued for seven weeks, the baby's appetite became very poor (the yeast was then given by spoon), it failed to gain in weight and in May manifested tenderness of the lower end of the femur. All these signs and symptoms yielded promptly when orange juice was substituted for yeast.

The second case was that of a baby who had been admitted to the institution when 16 days old, weighing 6½ pounds. It was fed on Schloss milk and weighed 9½ pounds when 3 months of age. From this time, however, it failed to gain, so that it was considered a favorable case for prescribing yeast. As will be noted (Chart 2), yeast was given three weeks without effect. A change was then made to orange

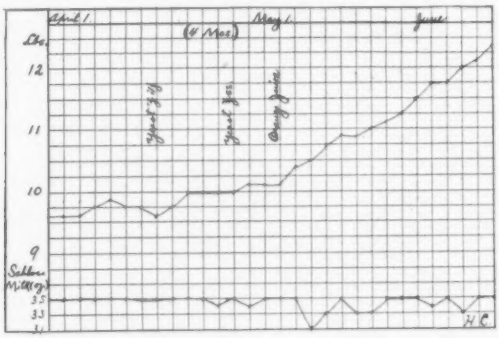

Chart 2.—Failure of yeast as a prophylactic; latent scurvy promptly yielding to orange juice.

juice, with the remarkable result noted in the chart, namely, a prompt gain in weight, although the consumption of food remained the same. In addition there was an improvement in the general condition and a subsidence of eczema of the face, a phenomenon noted in two other cases following the administration of orange juice. We regard this as a case of latent scurvy in an exceptionally young infant.

The third case relates to a baby who entered the institution when almost 6 weeks old, weighing 4¾ pounds. It did well on Schloss milk, and weighed 7¼ pounds at 3 months, and 8¾ at 4 months, when yeast was added to the diet. About two weeks later its weight curve began

2. Schloss milk is composed of 140 c.c. of milk, 140 c.c. of 20 per cent. cream, 35 gm. of dextrimaltose, 15 gm. of flour, 5 gm. of plasmon, 0.2 gm. of potassium chlorate and 700 c.c. of water. The milk and cream were pasteurized, and added to the other ingredients after they had been boiled for fifteen minutes and cooled.

to flatten. When 5 months old it contracted nasal diphtheria and its appetite was impaired. This infection yielded to antitoxin and the appetite improved. However, no gain in weight could be effected, even though cereal was added to the diet. The child was pale, had marked eczema of the neck and back, rapid respirations, tachycardia, and again loss of appetite. Orange juice was given, and all the symptoms abated, including the eczema and the cardiorespiratory disturbance.

In previous papers mention has been made of cases of mild scurvy developing on pasteurized milk. In two of these cases the autolyzed yeast was made use of to effect a cure. The one illustrated in Chart 3 is a case which was reported in detail in a recent paper treating of growth in scurvy[3] to illustrate the point that an infant who has been underfed may develop scurvy, notwithstanding a satisfactory gain in

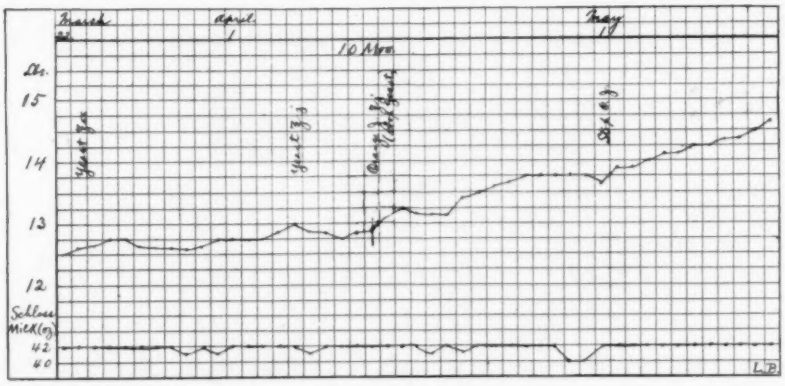

Chart 3.—Failure of yeast as a curative antiscorbutic.

weight. When this baby showed scorbutic signs, much to our surprise, as it had seemed to be progressing well, we attempted a cure by means of yeast. This was given for eighteen days, in daily quantity of one half ounce and later one ounce. The peridental hemorrhages, the pallor, the lack of gain, the rapid respiration, nevertheless, persisted. The hope of accomplishing a cure by this means was then abandoned and orange juice was substituted for the yeast. This resulted in a prompt disappearance of the hemorrhages and a coincident improvement in all the symptoms.

As regards the other case in which yeast was employed as a curative agent, little need be added to what is illustrated in Chart 8. It will be seen that in this case, that of a well-nourished infant, both egg yolk[4]

3. Hess, A. F.: Am. Jour. Dis. Child., 1916, **12,** 152.

4. According to McCollum and Davis egg contains both the fat and water soluble accessories for growth, Jour. Biol. Chem., November, 1915, **23,** 181.

and germ meal water were tried before the autolyzed yeast. Under the yeast therapy the appetite decreased rather than improved, the general symptoms and the periosteal tenderness became more marked, so that after a trial of four days we resorted to orange juice. This brought about a decided improvement within from twenty-four to forty-eight hours.

It will thus be seen that yeast failed signally as an antiscorbutic from a prophylactic as well as from a curative point of view. If it possesses this property at all, it is in too slight a degree to be recognized clinically, and negligible from a practical and therapeutic point of view. Although this result was discouraging and not what had been anticipated, it shows conclusively that however close disorders such as beriberi and infantile scurvy may be, they must be regarded, in a clinical as well as in a chemical sense, as due to substances which are therapeutically totally different.

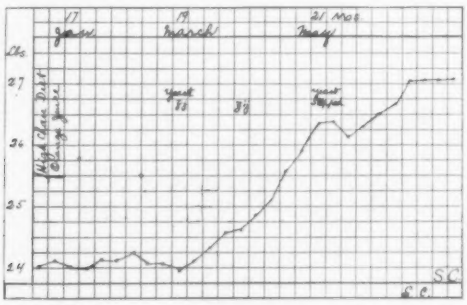

Chart 4.—Growth stimulated by means of autolyzed yeast in an older baby who had not gained for over two months.

Although yeast proved to possess little or no value as an antiscorbutic, it was found to be an excellent stimulant of growth. Thus the differentiation between an antiscorbutic and an essential growth stimulant—a distinction which was emphasized in the article in this series treating of growth in scurvy—was again substantiated. Following the addition of the yeast to the milk, there was in many instances a prompt rise in the weight curve. This sharp reaction led at first to the misconception that we were dealing with an excellent antiscorbutic substance. This inference was especially plausible in cases in which a gain was brought where none had taken place for weeks or months. But, as has been mentioned, the two phenomena were found to be by no means interdependent. In some instances infants gained 9 or 10 ounces the first week and then ceased to increase in weight; in others the gain was continued for several weeks. This favorable effect on growth was due, no doubt, in some cases to the stimulation of appetite, but in others there was a prompt response although the total intake of

food remained the same. The yeast also had a favorable effect on the digestive processes, as shown not only by an increase of appetite, but by the character of the stools, which in some instances became normal where previously they had been constipated or poorly digested.

After it had been found that autolyzed yeast stimulated the growth of infants, it was determined to attempt to stimulate the growth of some older babies, who had maintained an almost constant weight for a period of weeks and months, in spite of various changes of diet. These children were from 1½ to 2 years old, and received a diet of milk, cereal, vegetables and fruit, which is termed "high chair diet" in the institution. In some instances cod liver oil had been given without avail. Yeast was now added to the diet, either in the autolyzed form or as yeast powder, which is prepared by drying the compressed brewer's yeast. One half ounce of the latter was added to the cereal

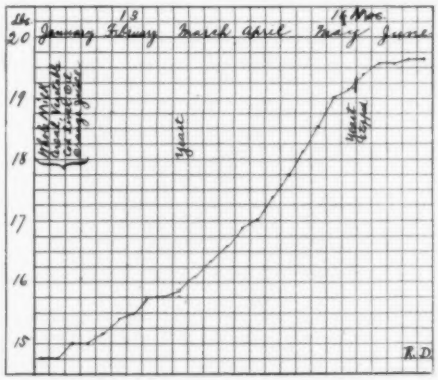

Chart 5.—Growth stimulated in an older baby by means of autolyzed yeast; gain of a pound in the two months previous to giving yeast, and of 2½ pounds in the subsequent two months.

or soup. It is unpalatable in whatever medium it is given, and although these children were successfully coaxed to take the prescribed amount, in many instances it was difficult to accomplish. Our results with these older infants were encouraging, as both the fluid and the dried yeast caused a definite gain in weight. This is well illustrated by Charts 4, 5, and 6, including two patients who received fluid yeast and one who was given the desiccated preparation.

In a previous paper treating more particularly of the relation of infantile scurvy and beriberi, mention was made of the use of wheat middlings as an antiscorbutic,[1] the subject being merely touched on and referred for detailed consideration to a later time. The wheat middlings were added to the wheat cereal (farina) in order to note its value as an antiscorbutic. In this connection a few words of explanation would seem in place. Farina is the starchy kernel of the wheat from which the outer layer has been removed. It has been repeatedly

shown that beriberi is brought about by a diet of overmilled rice, which has been deprived of the outer layer or pericarp. It has likewise been established that the addition of rice polishings to the food suffices to effect a rapid cure of beriberi in man, or of its counterpart, polyneuritis, in birds. In view of these facts and the clinical similarity between infantile scurvy and beriberi, we decided to substitute in place of the farina a cereal containing the outer layer of the wheat. To this end we prepared a food consisting of two parts of middlings (the pericarp of the wheat) and one part of flour, and gave this in place of farina. No other change whatsoever was made in the diet. In some instances of scurvy improvement was noted; however, this could not be compared to the miraculous change brought about when orange juice was given. Frequently the gain in weight was not maintained, and in some cases there was not a concomitant improvement in the general symptoms characteristic of a mild form of scurvy. It seemed as if the middlings contained a small amount of the essential antiscorbutic substance, the vitamins of Funk, but a quantity insufficient

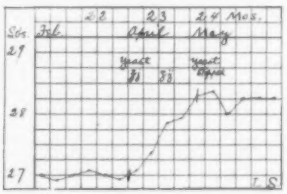

Chart 6.—Growth stimulated in an older baby by means of dried yeast; immobile weight for five weeks; gain of 1¼ pounds in the five weeks subsequent to giving yeast.

to reestablish an adequate positive balance of this material. In view of the excellent results obtained by McCollum and his co-workers with the germ or embryo of wheat, it was determined to prepare a cereal containing this substance instead of middlings, to add this germ meal cereal to the dietary of pasteurized milk, and to observe whether it would not act as a substitute for orange juice. It will be remembered that McCollum and his co-workers found that they could produce marked growth in rats by adding wheat germ to the diet, and claimed that the germ contains two active accessory substances, one soluble in fat and the other soluble in water and stable to heat.[5] They also found that 8 per cent. wheat bran was no more efficient than 4 per cent. wheat embryo in promoting growth. More recently Sullivan and Voegtlin have reported the presence of an antineuritic substance in wheat bran, which may be obtained by means of hydrolysis and proper fractionization.[6]

5. McCollum, E. V., and Davis, M.: Jour. Biol. Chem., November, 1915, **23,** 181.
6. Sullivan, M. X., and Voegtlin, C.: Jour. Biol. Chem., March, 1916.

Wheat embryo is particularly rich in fats, the preparation which we employed containing 10.9 per cent. of ether-soluble extract. It was found that a cereal composed of equal parts of wheat germ and of farina was too rich for infants to take for long periods, and that they soon lost their appetites and refused it. If, however, only one third of the germ meal was used, this loss of appetite did not ensue. Accordingly, a cereal was made of this composition, was cooked for two hours, as had been the custom, and was given twice a day in as large amounts as the individual infant would take, some consuming as much as eight or ten tablespoonfuls a day. The results may be summarized by the statement that this food was incapable of replacing orange juice and could not be relied on to prevent the development of subacute scurvy. The case represented in Chart 7 is illustrative of this point. Here we note an infant that received the germ meal when it was 6 months old, and notwithstanding, showed definite signs of subacute

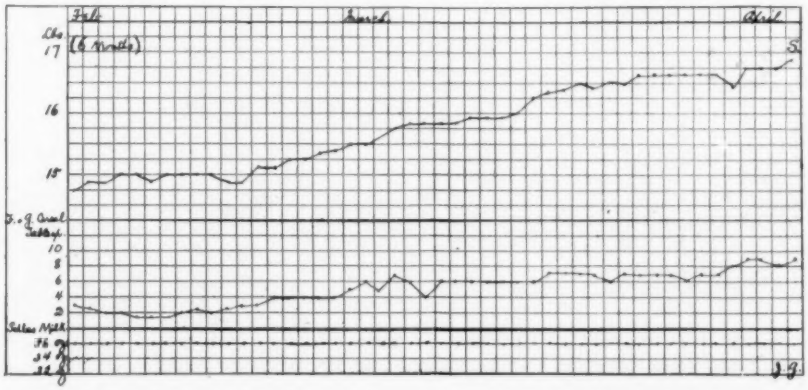

Chart 7.—Failure of wheat embryo as a prophylactic; development of subacute scurvy in a well-nourished infant despite gain in weight. (F. and G. cereal indicates farina and germ meal.)

scurvy, including tenderness and thickening of the lower end of the femur, three months later. This case is particularly interesting, as it illustrates the fact that an infant can gain in weight steadily while the scorbutic condition is slowly developing and advancing. In the last paper[3] an instance was cited, accompanied by a weight chart, of a baby previously underfed, who gained for weeks and months while developing scurvy. The present case shows that these apparently paradoxical phenomena may be concurrent in a well-nourished infant of normal weight who has received a sufficient quantity of food. Of the six infants placed on this cereal, three did satisfactorily, two showed some scorbutic signs, and a third appeared moderately well, but reacted later with a sharp gain in weight when orange juice was added to the diet, a reaction which we interpret as signifying that it had been receiving an insufficient amount of antiscorbutic foodstuff.

On Chart 8 it will be observed that "germ meal water" is recorded. This is an extract prepared somewhat after the method of the barley water, which is so commonly used in infant feeding; one tablespoonful of wheat germ meal is added to a pint of water, allowed to soak for two hours, and then boiled for two hours. We obtain in this way the water soluble substance of the germ meal, which, according to McCollum, has a remarkable growth stimulating effect, and is responsible for the cure in polyneuritis.[7] It will be seen that in this case giving the extract of the germ in addition to the cereal failed either to improve the appetite or to bring about a gain in weight; it may be added that it also failed to relieve the typical scorbutic symptoms. In some infants the addition of this germ meal water to the diet effected a sharp gain in weight, which was not the case, however, when the failure to gain was part of a scorbutic condition. Under ordinary circumstances stationary weight is to be regarded as a general nutritional

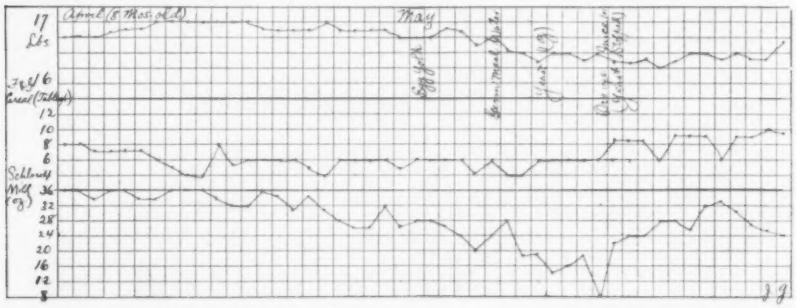

Chart 8.—Continuation of Chart 7; failure of egg yolk, germ meal extract and yeast as a curative antiscorbutic; improvement of appetite and general condition from orange juice.

disturbance; on the other hand, when it is due to scurvy it must be considered specific in character and only to be remedied by specific therapy. In this respect it resembles the specific serum therapy of the infectious diseases. In this case (Chart 8) it will be noted that although orange juice also failed to bring about a gain, it immediately stimulated the appetite, which had reached a very low ebb; furthermore, it caused a marked improvement in the general condition and well-being of the infant. As the result of our own experience with wheat embryo and with middlings, we are of the opinion that both contain a certain amount of antiscorbutic substance, and that the embryo contains a decidedly greater amount. In neither of these parts of the wheat is specific vitamin present in a concentration comparable to that of orange juice. It may be contended that the amount of the embryo which we made use of was inadequate. In a sense this may

7. McCollum, E. V., and Kennedy, C.: Jour. Biol. Chem., 1916, **24**, 491.

be true. However, from a dietetic point of view it is approximately as large a quantity as can be fed to infants.[8] Although the embryo cannot serve as antiscorbutic, there is a decided advantage in the use of germ meal cereal as well as of germ meal water, as they contain substance or substances which stimulate growth. There should be no misconception or confusion, however, as to their suitability, even in a prophylactic way, to replace orange juice. This is particularly to be regretted, as the preparation of a germ meal water which could be readily added to the milk instead of barley water would enable us to forego the necessity of giving our antiscorbutic food separately from the milk.

Charts 7, 8 and 9 show the daily weight for a period of six months of an infant who developed subacute scurvy, reproducing respectively the prescorbutic, the scorbutic and the reparative stages. In the second

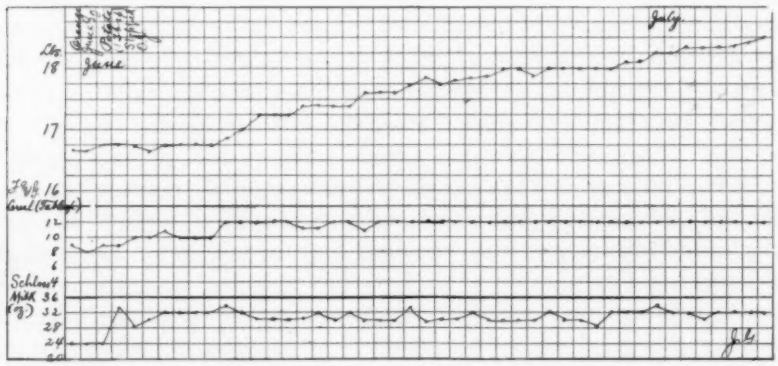

Chart 9.—Continuation of Chart 8; superior antiscorbutic effect of potato, in increasing appetite, in causing gain in weight and in improving the general condition.

of these charts (Chart 8) it will be seen that although orange juice increased the appetite, it could not bring about a gain in weight even after it had been taken for two weeks. It shows, furthermore, that when orange juice was discontinued and replaced by a tablespoonful of mashed potato (boiled), a steady increase in weight set in, accompanied by a marked stimulation of the appetite, more especially for the fluid food. Accompanying this change there was a decided improvement in the general condition. A reaction of this kind raises the question, not merely as to whether one of these antiscorbutics is the more potent, but as to possible qualitative differences among them, and

8. Each tablespoonful of the cereal contained 1 gm. of dried embryo, so that the average infant took about 8 gm. a day in this form. Each quart of Schloss milk contained about 21 gm. of the watery extract. It will thus be seen that the infant depicted in Chart 8 received from 10 to 15 gm. of this active substance in addition to the cereal.

whether one may not be better suited to the needs of one child than to those of another. This is a question to which, as may be imagined, it is at present impossible to give a direct answer.

It is evident, however, that in this particular case one tablespoonful of potato was clearly more potent than one or even two tablespoonfuls of orange juice. In the paper by Hess and Fish[9] two mild cases of scurvy were mentioned, which developed in spite of a diet including vegetables. Reports of other observers would also lead to the conclusion that some infants are unable thoroughly to utilize certain well-established antiscorbutics. There are, for example, undoubted cases scattered through the literature which developed despite the use of orange juice, just as there are others which have manifested themselves notwithstanding a diet of raw cow's milk, or even, most rare of all, of breast milk. Finkelstein's[10] well-known experience of infantile scurvy developing in two successive children of a family, although prophylactic measures were employed to avoid the occurrence in the second infant, is a striking example of the fact that a definite metabolic disturbance of this kind may exist in certain persons and families, which cannot be counterbalanced by specific therapy. It is conceivable that orange juice, potato, green vegetables and other antiscorbutic articles of diet do not supply entirely the same essential substances; that these substances differ slightly in their chemical constitution, or that one food may contain more than a single substance of this nature. The fact that in some cases of subacute scurvy, although we meet with a prompt reaction to orange juice, we find that this good effect is enhanced by substituting potato, a result which has been witnessed several times, or that the beneficial effect of orange juice is still further intensified when a vegetable is added to the dietary, may be accounted for in this way.

A question perhaps of more theoretical than practical interest is that of the power of the body to store the vitamins. It is generally believed, and seems the most plausible explanation, that infants do not develop scurvy during the first few months of life on account of the fund of antiscorbutic material which they have inherited from their mothers and brought with them into the world. If in postnatal life these substances are not supplied, a negative balance ensues and infantile scurvy gradually results. An observation which we were in a position to make leads us to believe that the tissues have a remarkable power for storing antiscorbutic vitamins. The case is the one previously reported: an infant who had been markedly underfed before entering the institution and who gained for some months after admission, but then showed signs of subacute scurvy, such as periosteal

9. Hess, A. F., and Fish, M.: Am. Jour. Dis. Child., 1914, **8**, 385.
10. Finkelstein, H.: Lehrbuch der Säuglingskrankheit, 1912, **2**, 480.

tenderness, pallor, peridental hemorrhage, and tachycardia. One ounce of orange juice was given for a period of sixteen days, in other words, a pint in all. By this time the scorbutic symptoms were relieved, the hemorrhages into the gums were no longer to be seen, and the general condition was greatly improved; accordingly, the antiscorbutic diet was discontinued. This was the first of May. The infant weighed almost 14 pounds at this time, and was nearly 11 months old. During May he gained three quarters of a pound. Farina was then added to his diet, besides the 42 ounces of Schloss milk. In June he gained about 1½ pounds. He gained nothing in July, but showed no signs of scurvy. In August 1 ounce of orange was again given daily. Although no greater amount of food was consumed, there was at once an increase in weight, a gain of 12 ounces during the first week and an improvement in the general condition. We interpret these phenomena as indicating that the sixteen months of orange juice had protected the child for a period of two months and that he then lapsed into a condition of latent scurvy. A negative balance of vitamins was evident from the child's nutritional stagnation, considered in conjunction with the prompt growth reaction on the administration of orange juice.

CONCLUSIONS

As it had been shown that a clinical similarity exists between beriberi and infantile scurvy, it seemed as if yeast, which is a specific in the former disease, might also prove to be a potent antiscorbutic. Clinical experience did not substantiate the analogy, but demonstrated that this substance is of no value in scurvy either as a prophylactic or as a curative dietetic agent. It was found, however, to possess virtue as a stimulant to growth, when added to the milk in the form of the fluid autolyzed yeast or given to older infants as a desiccated powder.

The embryo or germ of the wheat seed is another effective therapeutic agent in the cure of beriberi or in avian polyneuritis. Accordingly, this was also tested clinically for its antiscorbutic power; for this purpose a cereal and a watery extract of the germ meal were prepared. These preparations manifested some value as antiscorbutics, but not sufficient to render them useful in this connection from a practical or clinical standpoint. The watery extract, which is readily prepared, was found to stimulate growth, and may be used to advantage, on account of this quality, as a substitute for barley in milk preparations.

It was furthermore noted that there is an idiosyncracy as to the reaction to well-established antiscorbutics; for example, in some instances orange juice may meet with only partial success while potato produces a rapid cure.

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